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(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DEMONT, Emmanuel, Hubert** [FR/GB]; GlaxoSmithKline, The Frythe, Welwyn Hertfordshire AL6 9AR (GB). **REDSHAW, Sally** [GB/GB]; GlaxoSmithKline, The Frythe, Welwyn Hertfordshire AL6 9AR (GB). **WALTER, Daryl, Simon** [GB/GB]; GlaxoSmithKline, The Frythe, Welwyn Hertfordshire AL6 9AR (GB).

(74) Agent: **GIBSON, Mark**; GlaxoSmithKline (CN925.1), 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

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(54) Title: NOVEL COMPOUNDS

(57) Abstract: The present invention relates to novel hydroxyethylamine compounds having Asp2 (β-secretase, BACE1 or Memapsin) inhibitory activity, processes for their preparation, to compositions containing them and to their use in the treatment of diseases characterised by elevated β- amyloid levels or β-amyloid deposits, particularly Alzheimer's disease.

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NOVEL COMPOUNDS

The present invention relates to novel hydroxyethylamine compounds having Asp2 (β-secretase, BACE1 or Memapsin) inhibitory activity, processes for their preparation, to compositions containing them and to their use in the treatment of diseases characterised by elevated β- amyloid levels or β-amyloid deposits, particularly Alzheimer's disease.

Alzheimer's disease is a degenerative brain disorder in which extracellular deposition of β-amyloid (Aβ) in the form of senile plaques represents a key pathological hallmark of the disease (Selkoe, D. J. (2001) Physiological Reviews **81**: 741-766). The presence of senile plaques is accompanied by a prominent inflammatory response and neuronal loss. Aβ exists in soluble and insoluble, fibrillar forms and a specific fibrillar form has been identified as the predominant neurotoxic species (Vassar, R. and Citron, M. (2000) Neuron **27**: 419-422). In addition it has been reported that dementia correlates more closely with the levels of soluble amyloid rather than plaque burden (Naslund, J. *et al.* (2000) J. Am. Med. Assoc. **12**: 1571-1577; Younkin, S. (2001) Nat. Med. **1**: 8-19). Aβ is known to be produced through the cleavage of the beta amyloid precursor protein (also known as APP) by an aspartyl protease enzyme known as Asp2 (also known as β-secretase, BACE1 or Memapsin) (De Strooper, B. and Konig, G. (1999) Nature **402**: 471-472).

Therefore, it has been proposed that inhibition of the Asp2 enzyme would reduce the level of APP processing and consequently reduce the levels of Aβ peptides found within the brain. Therefore, it is also thought that inhibition of the Asp2 enzyme would be an effective therapeutic target in the treatment of Alzheimer's disease.

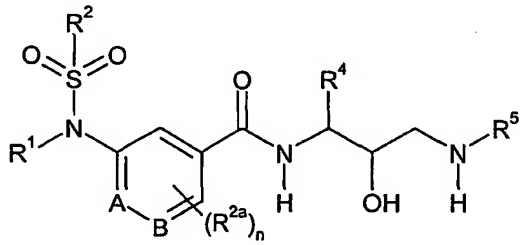
APP is cleaved by a variety of proteolytic enzymes (De Strooper, B. and Konig, G. (1999) Nature **402**: 471-472). The key enzymes in the amyloidogenic pathway are Asp2 (β-secretase) and γ-secretase both of which are aspartic proteinases and cleavage of APP by these enzymes generates Aβ. The non-amyloidogenic, α-secretase pathway, which precludes Aβ formation, has been shown to be catalysed by a number of proteinases, the best candidate being ADAM10, a disintegrin and metalloproteinase. Asp1 has been claimed to show both α- and β-secretase activity *in vitro*. The pattern of expression of Asp1 and Asp2 are quite different, Asp2 is most highly expressed in the pancreas and brain while Asp1 expression occurs in many other peripheral tissues. The Asp2 knockout mouse indicates that lack of Asp2 abolished Aβ production and also shows that in this animal model endogenous Asp1 cannot substitute for the Asp2 deficiency (Luo, Y. *et al.* (2001) Nat Neurosci. **4**: 231-232; Cai, H. *et. al.* (2001) Nat Neurosci. **4**: 233-234; Roberds, S. L. *et al.* (2001) Hum. Mol. Genet. **10**: 1317-1324).

For an agent to be therapeutically useful in the treatment of Alzheimer's disease it is preferable that said agent is a potent inhibitor of the Asp2 enzyme, but should ideally also be selective for Asp2 over other enzymes of the aspartyl proteinase family, e.g Cathepsin D (Connor, G. E. (1998) Cathepsin D in Handbook of Proteolytic Enzymes, Barrett, A. J., Rawlings, N. D., & Woesner, J. F. (Eds) Academic Press London. pp828-836).

WO 01/70672, WO 02/02512, WO 02/02505 and WO 02/02506 (Elan Pharmaceuticals Inc.) describe a series of hydroxyethylamine compounds having β-secretase activity which are implicated to be useful in the treatment of Alzheimer's disease.

We have found a novel series of compounds which are potent inhibitors of the Asp2 enzyme, thereby indicating the potential for these compounds to be effective in the treatment of disease characterised by elevated β-amyloid levels or β-amyloid deposits, such as Alzheimer's disease.

Thus, according to a first aspect of the present invention we provide a compound of formula (I):



(I)

wherein

R^1 represents aryl or heteroaryl;

R^2 represents C_{1-6} alkyl or C_{3-8} cycloalkyl;

R^{2a} represents hydrogen, halogen, C_{1-3} alkyl or C_{1-3} alkoxy;

n represents 0, 1 or 2;

A represents –C(H)=, -C(R^{2b})= or –N=;

R^{2b} represents C_{1-3} alkyl, C_{2-4} alkenyl, halogen, C_{1-3} alkoxy, amino, cyano or hydroxy;

B represents –C(R^3)= or –N=;

R^3 represents hydrogen, halogen, optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl, -C_{2-6} alkenyl-aryl, -C_{2-6} alkenyl-heteroaryl, -C_{2-6} alkenyl-heterocyclyl, C_{3-8} cycloalkyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, cyano, azido, nitro, sulphoxide, –NR^7R^8, -NR^9COR^{10}, -$NR^{11}SO_2R^{12}$, -$NR^{11}CO_2R^{12}$, -OR^{13}, -SO_2R^{14}, -SR^{15}, -C≡CR^{16}, -C_{0-6} alkyl-$(CF_2)_qCF_3$, -$CONR^{17}R^{18}$, $COOR^{19}$, -C_{1-6} alkyl-$NR^{20}R^{21}$ or -C_{1-6} alkyl-N_3, or R^3 together with R^{2b} on adjacent carbon atoms may form a fused 5-7 membered saturated or partially saturated carbocyclic or heterocyclic ring optionally substituted by a C_{1-6} alkyl group;

R^4 represents optionally substituted C_{1-6} alkyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl or -C_{1-6} alkyl-heterocyclyl;

R^5 represents hydrogen, optionally substituted C_{1-10} alkyl, -C_{3-8} cycloalkyl, -C_{3-8} cycloalkenyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, -C_{3-8} cycloalkyl-aryl, -heterocyclyl-aryl, -C_{1-6} alkyl-aryl-heteroaryl, -$C(R^aR^b)$-CONH-C_{1-6} alkyl, -$C(R^cR^d)$-CONH-C_{3-8} cycloalkyl, -C_{2-6} alkyl-S-C_{1-6} alkyl, -C_{2-6} alkyl-NR^eR^f, -$C(R^gR^h)$-C_{1-6} alkyl, -$C(R^iR^j)$-aryl, -$C(R^kR^l)$-C_{1-6} alkyl-aryl, -$C(R^mR^n)$-C_{1-6} alkyl-heteroaryl, -$C(R^oR^p)$-C_{1-6} alkyl-heterocyclyl, -C_{1-6} alkyl-O-C_{1-6} alkyl-aryl, -C_{1-6} alkyl-O-C_{1-6} alkyl-heteroaryl or -C_{1-6} alkyl-O-C_{1-6} alkyl-heterocyclyl;

R^7, R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20} and R^{21} independently represent hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, -CO-C_{1-6} alkyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl or -C_{1-6} alkyl-heterocyclyl;

R^a, R^c, R^e, R^f, R^g, R^h, R^i, R^j, R^k, R^l, R^m, R^n, R^o and R^p independently represent hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl;

R^b and R^d independently represent hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl or -C_{1-6} alkyl-SO_2-C_{1-6} alkyl or R^a and R^b, R^c and R^d, R^g and R^h, R^i and R^j, R^k and R^l and R^m and R^n together with the carbon atom to which they are attached may form a C_{3-8} cycloalkyl group;

R^{12} represents C_{1-6} alkyl or C_{3-8} cycloalkyl;

q represents 0 to 3;

optional substituents for alkyl groups of R^3, R^4 and R^5 include one or more (eg. 1, 2 or 3) halogen, C_{1-6} alkoxy, amino, cyano or hydroxy groups;

and wherein said aryl, heteroaryl or heterocyclyl groups may be optionally substituted by one or more (eg. 1, 2 or 3) C_{1-6} alkyl, halogen, -CF_3, -OCF_3, =O, hydroxy, C_{1-6} alkoxy, C_{2-6} alkynyl, C_{2-6} alkenyl, amino, cyano, nitro, -$NR^{22}COR^{23}$, –$CONR^{22}R^{23}$ -C_{1-6} alkyl-NR^{22} R^{23} (wherein R^{22} and R^{23} independently represent hydrogen or C_{1-6} alkyl), -C_{1-6} alkyl-O-C_{1-6} alkyl or -C_{1-6} alkanoyl groups;

or a pharmaceutically acceptable salt or solvate thereof.

In one particular aspect of the present invention, there is provided a compound of formula (I) as defined above wherein:

R^2 represents C_{1-6} alkyl; and

R^{2a} represents hydrogen, halogen or C_{1-3} alkyl; and

R^3 represents hydrogen, halogen, optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl, -C_{2-6} alkenyl-aryl, -C_{2-6} alkenyl-heteroaryl, -C_{2-6} alkenyl-heterocyclyl, C_{3-8} cycloalkyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, cyano, azido, nitro, sulphoxide, –NR^7R^8, -NR^9COR^{10}, -$NR^{11}SO_2R^{12}$, -OR^{13}, -SO_2R^{14}, -SR^{15}, -C≡CR^{16}, -C_{0-6} alkyl-$(CF_2)_qCF_3$, -$CONR^{17}R^{18}$, $COOR^{19}$, -C_{1-6} alkyl-$NR^{20}R^{21}$ or -C_{1-6} alkyl-N_3, or R^3 together with R^{2b} on adjacent carbon atoms may form a fused 5-7 membered saturated or partially saturated carbocyclic or heterocyclic ring; and

R^5 represents hydrogen, optionally substituted C_{1-10} alkyl, -C_{3-8} cycloalkyl, -C_{3-8} cycloalkenyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, -C_{3-8} cycloalkyl-aryl, -heterocyclyl-aryl, -C_{1-6} alkyl-aryl-heteroaryl, -$C(R^aR^b)$-CONH-C_{1-6} alkyl, -$C(R^cR^d)$-CONH-C_{3-8} cycloalkyl, -C_{1-6} alkyl-S-C_{1-6} alkyl, -C_{1-6} alkyl-NR^eR^f, -$C(R^gR^h)$-C_{1-6} alkyl, -$C(R^iR^j)$-aryl, -$C(R^kR^l)$-C_{1-6} alkyl-aryl, -$C(R^mR^n)$-C_{1-6} alkyl-heteroaryl, -$C(R^oR^p)$-C_{1-6} alkyl-heterocyclyl, -C_{1-6} alkyl-O-C_{1-6} alkyl-aryl, -C_{1-6} alkyl-O-C_{1-6} alkyl-heteroaryl or -C_{1-6} alkyl-O-C_{1-6} alkyl-heterocyclyl; and

R^{11}, R^a, R^c, R^e, R^f, R^g, R^h, R^i, R^j, R^k, R^l, R^m, R^n, R^o and R^p independently represent hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl; and

q represents 1 to 3.

References to alkyl include references to both straight chain and branched chain aliphatic isomers of the corresponding alkyl. It will be appreciated that references to alkenyl shall be interpreted similarly.

References to C_{3-8} cycloalkyl include references to all alicyclic (including branched) isomers of the corresponding alkyl.

References to 'aryl' include references to monocyclic carbocyclic aromatic rings (eg. phenyl) and bicyclic carbocyclic aromatic rings (e.g. naphthyl) or carbocyclic benzofused rings (eg. C_{3-8} cycloalkyl fused to a phenyl ring).

References to 'heteroaryl' include references to mono- and bicyclic heterocyclic aromatic rings containing 1-4 hetero atoms selected from nitrogen, oxygen and sulphur. Examples of monocyclic heterocyclic aromatic rings include e.g. thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl, pyridyl, tetrazolyl and the like. Examples of bicyclic heterocyclic aromatic rings include eg. quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.

References to 'heterocyclyl' include references to a 5-7 membered non-aromatic monocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen. Examples of heterocyclic non-aromatic rings include e.g. morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl, oxathianyl, dithianyl, dioxanyl, pyrrolidinyl, dioxolanyl, oxathiolanyl, imidazolidinyl, pyrazolidinyl and the like.

Preferably, R^1 represents aryl (eg. phenyl or naphthyl) or heteroaryl (eg. pyridyl) optionally substituted by one or more halogen (eg. fluorine or chlorine), cyano, -CF_3, C_{1-6} alkoxy (eg. methoxy) or $-CONR^{22}R^{23}$ (eg. $-CONH_2$) groups.

More preferably, R^1 represents aryl (eg. phenyl or naphthyl) or heteroaryl (eg. pyridyl) optionally substituted by one or more halogen (eg. fluorine or chlorine) atoms.

Most preferably, R^1 represents aryl, eg. unsubstituted phenyl or phenyl substituted by a halogen (eg. fluorine or chlorine), cyano, or C_{1-6} alkoxy (eg. methoxy) group.

Preferably, R^2 represents methyl, ethyl, i-propyl or butyl, more preferably methyl.

Preferably, n is 0 or 1, more preferably 1.

When n represents 1, R^{2a} is preferably C_{1-3} alkyl (eg. methyl) or halogen (eg. fluorine), more preferably halogen (eg. fluorine).

When n represents 1, R^{2a} is preferably at the para position of the carbocyclic/heterocyclic ring with respect to the group B.

When A represents $-C(R^{2b})=$, R^{2b} is preferably:
halogen (eg. chlorine or fluorine); or
C_{1-3} alkyl (eg. methyl).

When A represents $-C(R^{2b})=$, R^{2b} is more preferably fluorine.

Preferably, A represents –C(H)= or -N=, more preferably –C(H)=.

Preferably, B represents $-C(R^3)=$.

Preferably, R^3 represents:
halogen (eg. bromine);
C_{1-6} alkyl (eg. ethyl, propyl, i-propyl or t-butyl);
C_{2-6} alkenyl (eg. $-CH=CH_2$, $-CH=C(CH_3)_2$, $-CH(CH_3)=CH_2$ or $-CH=CH-CH_3$);
C_{3-8} cycloalkyl (eg. cyclopentyl or cyclohexyl);
cyano;
aryl (eg. phenyl) optionally substituted by one or more C_{1-6} alkyl (eg. methyl) groups;
heterocyclyl (eg. pyrrolidinyl or isothiazolidinyl) optionally substituted by one or two oxo groups (eg. 2-oxopyrrolidinyl or 1,1-dioxo-isothiazolidinyl);
$-NR^7R^8$;
$-OR^{13}$;
$-SO_2R^{14}$;
$-SR^{15}$;
$-C\equiv CR^{16}$; or
$-CONR^{17}R^{18}$.

Also preferably, R^3 together with R^{2b} on adjacent carbon atoms forms a partially saturated heterocyclic (eg. pyrroline) group optionally substituted by a C_{1-6} alkyl group (eg. ethyl).

More preferably, R^3 represents:

halogen (eg. bromine);
C_{1-6} alkyl (eg. i-propyl);
C_{2-6} alkenyl (eg. $-CH=CH_2$, $-CH=C(CH_3)_2$, $-CH(CH_3)=CH_2$ or $-CH=CH-CH_3$);
C_{3-8} cycloalkyl (eg. cyclopentyl);
$-NR^7R^8$;
$-OR^{13}$;
$-SR^{15}$; or
heterocyclyl (eg. pyrrolidinyl) substituted by an oxo group (eg. 2-oxopyrrolidinyl).

Preferably, R^7 and R^8 independently represent:

hydrogen;
C_{1-6} alkyl (eg. methyl, ethyl, propyl, butyl, pentyl, i-propyl, i-butyl, ethylpropyl, dimethylpropyl or methylbutyl);
C_{3-8} cycloalkyl (eg. cyclopentyl or cyclohexyl);
aryl (eg. phenyl);
$-C_{1-6}$ alkyl-C_{3-8} cycloalkyl (eg. $-CH_2$-cyclopropyl);
$-C_{1-6}$ alkyl-aryl (eg. $-CH_2$-phenyl or $-(CH_2)_2$-phenyl); or
$-CO-C_{1-6}$ alkyl (eg. $-COCH_3$).

More preferably, R^7 and R^8 independently represent hydrogen, C_{1-6} alkyl (eg. methyl, ethyl or isopropyl) or $-C_{1-6}$ alkyl-aryl (eg. $-CH_2$-phenyl), especially hydrogen or C_{1-6} alkyl.

Most preferably, R^7 represents hydrogen and R^8 represents C_{1-6} alkyl (eg. ethyl or isopropyl).

Preferably, R^{13} represents C_{1-6} alkyl (eg. ethyl or isopropyl).

Preferably, R^{14} and R^{15} independently represent C_{1-6} alkyl (eg. methyl or ethyl).

More preferably, R^{15} represents ethyl.

Preferably, R^{16} represents hydrogen or C_{1-6} alkyl (eg. methyl).

Preferably, R^{17} and R^{18} independently represent C_{1-6} alkyl (eg. propyl).

Preferably, R^4 represents -C_{1-6} alkyl-aryl (eg. benzyl) optionally substituted by one or two halogen atoms (eg. fluorine). More preferably, R^4 represents unsubstituted benzyl.

Preferably, R^5 represents:

-C_{1-10} alkyl (eg. 1,5-dimethylhexyl or 1,1,5-trimethylhexyl);

-C_{3-8} cycloalkyl (eg. cyclopropyl or cyclohexyl);

-$C(R^iR^j)$-aryl (eg. benzyl or 1-phenyl-1-methylethyl) optionally substituted (eg. substituted at the 3 and 5 positions) by one or more halogen, cyano, -OCF_3, -CF_3, C_{1-6} alkyl or C_{1-6} alkoxy (eg. methoxy) groups;

-$C(R^cR^d)$-CONH-C_{3-8} cycloalkyl (eg. $C(R^cR^d)$-CONH-cyclohexyl); or

-C_{3-8} cycloalkyl-aryl.

More preferably, R^5 represents:

-$C(R^iR^j)$-aryl (eg. benzyl) optionally substituted by an -OCF_3 or -CF_3 group; or

-$C(R^cR^d)$-CONH-C_{3-8} cycloalkyl (eg. $C(R^cR^d)$-CONH-cyclohexyl).

Preferably, R^c and R^d independently represent hydrogen or methyl, more preferably R^c represents hydrogen and R^d represents methyl.

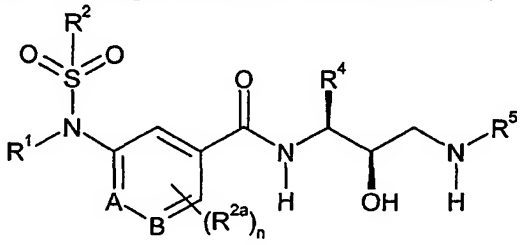
Preferably, R^i and R^j independently represent hydrogen or C_{1-6} alkyl (eg. methyl) or together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl group.

Preferred compounds according to the invention includes examples E1-E90 as shown below, or a pharmaceutically acceptable salt thereof.

The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, **66**, 1-19, such as acid addition salts formed with inorganic or organic acids e.g. hydrochlorides, hydrobromides, sulphates, phosphates, acetates, benzoates, citrates, nitrates, succinates, lactates, tartrates, fumarates, maleates, 1-hydroxy-2-naphthoates, palmoates, methanesulphonates, p-toluenesulphonates, naphthalenesulphonates, formates or trifluoroacetates. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be solvated, eg. as the hydrate. This invention includes within its scope stoichiometric solvates (eg. hydrates) as well as compounds containing variable amounts of solvent (eg. water).

Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof. Preferably, compounds of formula (I) are in the form of a single enantiomer of formula (Ia):

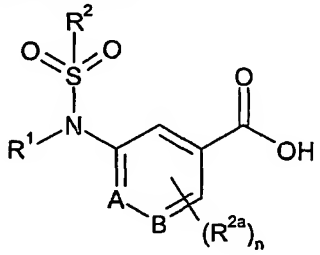


(Ia)

The compounds of formula (I) and salts and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

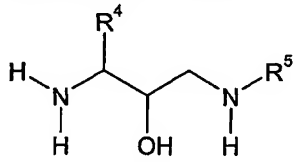
A process according to the invention for preparing a compound of formula (I) which comprises:

(a) reacting a compound of formula (II)



(II)

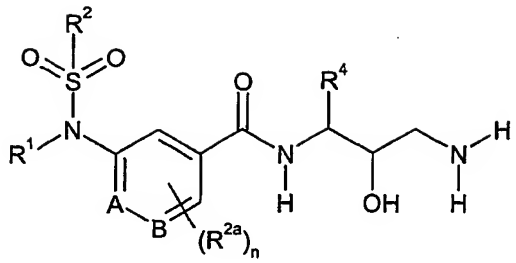
or an activated and/or optionally protected derivative thereof wherein R^1, R^2, R^{2a}, n, A and B are as defined above, with a compound of formula (III)



(III)

wherein R^4 and R^5 are as defined above; or

(b) preparing a compound of formula (I) which comprises reductive alkylation of a compound of formula (IV)



(IV)

wherein R^1, R^2, R^{2a}, n, A, B and R^4 are as defined above, with an appropriate aldehyde or ketone; or

(c) deprotecting a compound of formula (I) which is protected; and optionally thereafter

(d) interconversion of compounds of formula (I) to other compounds of formula (I).

Where the compound of formula (II) is an activated derivative, (eg. by activation of a carboxylic acid to an acid chloride, mixed anhydride, active ester e.g. mesylate or tosylate, O-acyl-isourea or other species), process (a) typically comprises treatment of said activated derivative with an amine (Ogliaruso, M.A.; Wolfe, J.F. in *The Chemistry of Functional Groups (Ed. Patai, S.) Suppl. B: The Chemistry of Acid Derivatives, Pt. 1* (John Wiley and Sons, 1979), pp 442-8; Beckwith, A.L.J. in *The Chemistry of Functional Groups (Ed. Patai, S.) Suppl. B: The Chemistry of Amides (Ed. Zabricky, J.)* (John Wiley and Sons, 1970), p 73 ff. The acid of formula (II) and amine are preferably reacted in the presence of an activating agents such as 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBT), or O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU)

Where the compound of formula (II) is a carboxylic acid, process (a) typically comprises the use of water soluble carbodiimide, HOBT and a suitable base such as tertiary alkylamine or pyridine in a suitable solvent such as DMF and at a suitable temperature, eg. between 0°C and room temperature.

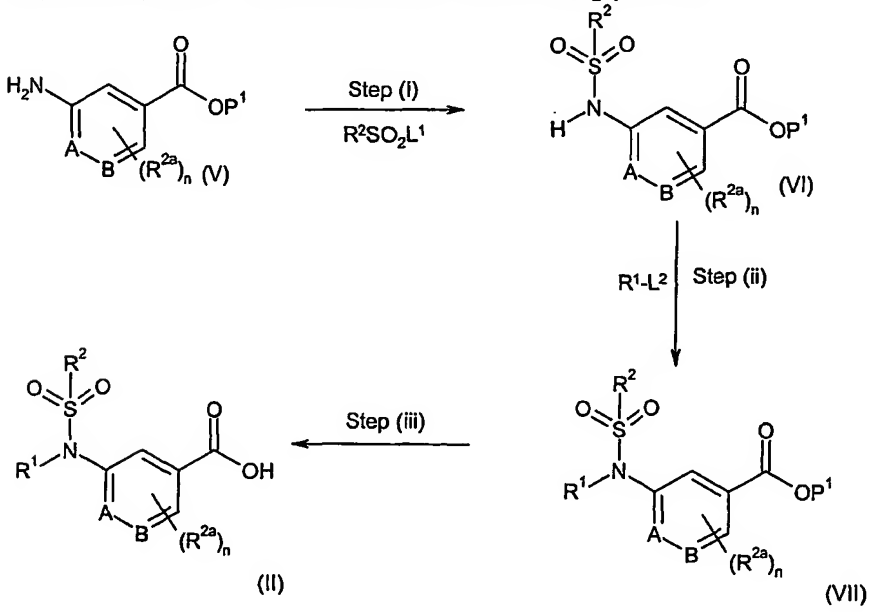
Process (b) typically comprises the use of sodium borohydride triacetate in the presence of a suitable solvent, such as ethanol, dichloromethane and 1,2-dichloroethane and at a suitable temperature, e.g. between 0°C and room temperature.

In process (c), examples of protecting groups and the means for their removal can be found in T. W. Greene and P.G.M. Wuts 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 3rd Ed. 1999). Suitable amine protecting groups include aryl sulphonyl (e.g. tosyl), acyl (e.g. acetyl), carbamoyl (e.g. benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis or hydrogenolysis as

appropriate. Other suitable amine protecting groups include trifluoroacetyl (-$COCF_3$) which may be removed by base catalysed hydrolysis. Suitable hydroxy protecting groups would be silyl based groups such as t-butyldimethylsilyl, which may be removed using standard methods, for example use of an acid such as trifluoroacetic or hydrochloric acid or a fluoride source such as tetra n-butylammonium fluoride.

Process (d) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, aromatic substitution, ester hydrolysis, amide bond formation or removal and sulphonylation. An example of such an interconversion reaction may include interconversion of a compound of formula (I) wherein B represents –$C(R^3)$= and R^3 represents a C_{2-6} alkenyl containing group to a corresponding compound of formula (I) wherein R^3 represents a C_{2-6} alkyl containing group, using standard hydrogenation or reductive conditions. A further example of such an interconversion reaction may include interconversion of a compound of formula (I) wherein R^3 represents - C_{1-6} alkyl-N_3 to a corresponding compound of formula (I) wherein R^3 represents -C_{1-6} alkyl-NH_2, using standard hydrogenation or reductive conditions. A yet further example of such an interconversion reaction may include interconversion of a compound of formula (I) wherein R^3 represents a nitro group to a corresponding compound of formula (I) wherein R^3 represents NH_2, using standard hydrogenation or reductive conditions. A yet further example of such an interconversion reaction may include interconversion of a compound of formula (I) wherein R^3 represents a halogen atom to a corresponding compound of formula (I) wherein R^3 represents a C_{2-6} alkenyl group, using standard Suzuki coupling conditions.

Compounds of formula (II) and/or activated and optionally protected derivatives thereof may be prepared in accordance with the following process:



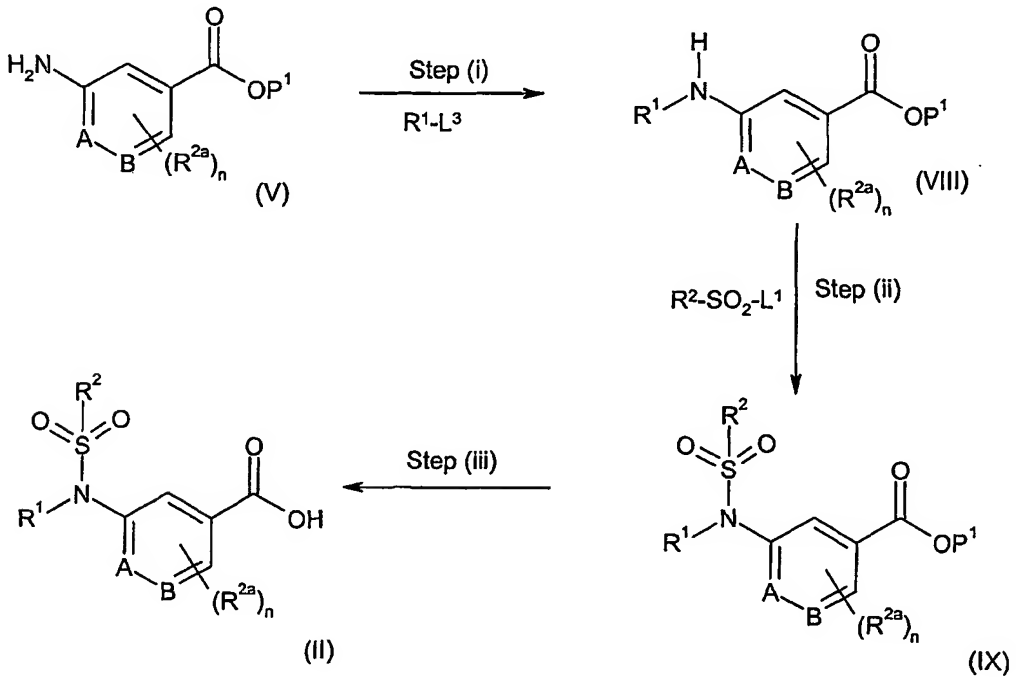
wherein R^{2a}, n, A, B, R^1 and R^2 are as defined above, P^1 represents a suitable group such as C_{1-6} alkyl, L^1 represents a suitable leaving group such as a halogen atom (eg. iodine, chlorine or bromine) and L^2 represents a suitable group such as boronic acid or a boronic ester.

Step (i) typically comprises the use of a suitable solvent such as dichloromethane and suitable bases such as pyridine and dimethylaminopyridine at a suitable temperature, such as room temperature.

Step (ii) typically comprises the use of copper (II) acetate in the presence of a suitable solvent such as dichloromethane and a suitable base such as triethylamine at a suitable temperature, such as room temperature (Chan *et al*, (1998) Tetrahedron Letters **39**, 2933-2936).

Step (iii) typically comprises a standard procedure for conversion of a carboxylic ester to an acid, such as the use of an appropriate hydroxide salt like lithium or sodium salt in an appropriate solvent such as methanol at an appropriate temperature such as room temperature. In the case of a tert-butyl ester this conversion can be achieved by the use of an appropriate acid such as trifluoroacetic acid in an appropriate solvent such as dichloromethane at an appropriate temperature such as O°C. Activated derivatives of compounds of formula (II) may then be prepared as described in process (a) above.

Compounds of formula (II) or activated and optionally protected derivatives thereof may also be prepared in accordance with the following process:



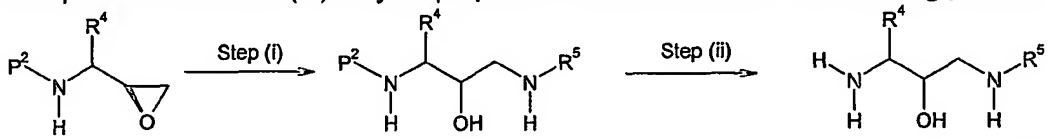
wherein R^{2a}, n, A, B, R^1, R^2, P^1 and L^1 are as defined above and L^3 represents a suitable leaving group such as a halogen atom (eg. bromine, chlorine or iodine), $OSO_2(CF_2)_{0-7}CF_3$.

Step (i) typically comprises the use of caesium carbonate, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene and a suitable catalyst such as tris(dibenzylideneacetone)dipalladium(0) in the presence of a suitable solvent (eg. toluene) at a suitable temperature, eg. 100°C.

Step (ii) typically comprises the use of lithium diisopropylamide in the presence of a suitable solvent such as tetrahydrofuran at a suitable temperature, eg. heating from -78°C to room temperature.

Step (iii) typically comprises a standard procedure for conversion of a carboxylic ester to an acid, such as the use of an appropriate hydroxide salt such as lithium or sodium salt in an appropriate solvent such as methanol at an appropriate temperature such as room temperature. In the case of a tert-butyl ester this conversion can be achieved by the use of an appropriate acid such as trifluoroacetic acid in an appropriate solvent such as dichloromethane at an appropriate temperature such as 0°C. Activated derivatives of compounds of formula (II) may then be prepared as described in process (a) above.

Compounds of formula (III) may be prepared in accordance with the following process:



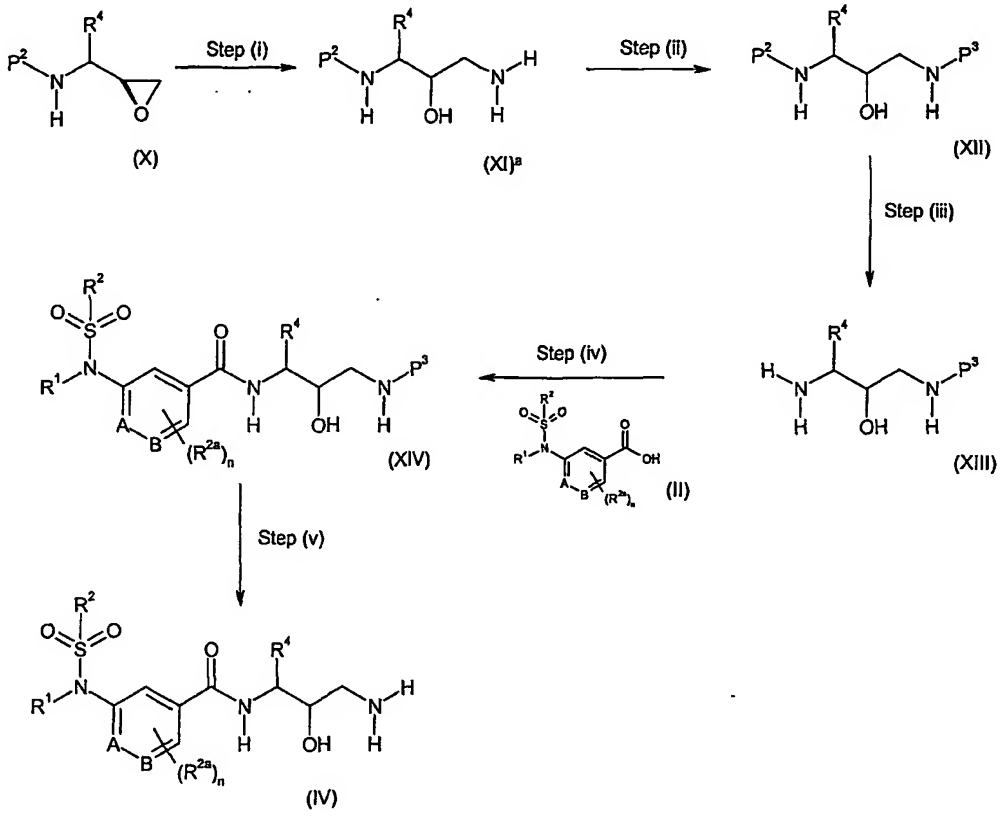
(X) (XI) (III)

wherein R^4 and R^5 are as defined above and P^2 represents a suitable amine protecting group, such as t-butoxycarbonyl.

Step (i) typically comprises the reaction of a compound of formula (X) with a compound of formula NH_2R^5 in the presence of a suitable solvent, e.g. ethanol at a suitable temperature, e.g. reflux.

Step (ii) typically comprises the use of suitable deprotection reactions as described above for process (c), eg. when P^2 represents t-butoxycarbonyl, deprotection typically comprises the use of trifluoroacetic acid in the presence of a suitable solvent, such as dichloromethane at a suitable temperature, e.g. between 0°C and room temperature.

Compounds of formula (IV) may be prepared in accordance with the following process:



wherein R^1, R^2, R^{2a}, n, A, B, R^4 and P^2 are as defined above and P^3 represents a suitable amine protecting group different to P^2, such as -$COOCH_2$-phenyl.

Step (i) typically comprises the reaction of a compound of formula (X) in aqueous ammonia in the presence of a suitable solvent, e.g. ethanol at a suitable temperature, e.g. reflux.

When P^3 represents -$COOCH_2$-phenyl, step (ii) typically comprises the use of $ClCOOCH_2$-phenyl in the presence of a suitable base, e.g. triethylamine, a suitable solvent, e.g. dimethylformamide at a suitable temperature, e.g. between 0°C and room temperature.

Step (iii) typically comprises the use of suitable deprotection reactions as described above for process (c), eg. when P^2 represents t-butoxycarbonyl, deprotection typically comprises the use of trifluoroacetic acid in the presence of a suitable solvent, such as dichloromethane at a suitable temperature, e.g. between 0°C and room temperature.

Step (iv) typically comprises reacting a compound of formula (XIII) with a compound of formula (II) in the presence of water soluble carbodiimide and HOBT.

Step (v) typically comprises the use of suitable deprotection reactions as described above for process (c), eg. when P^3 represents -$COOCH_2$-phenyl, deprotection typically comprises the use of a suitable catalyst, eg. palladium in the presence of a suitable solvent, e.g. water and ethanol and in the presence of a suitable hydrogen source, e.g. ammonium formate at a suitable temperature, eg. 60°C.

Compounds of formula (V) are either commercially available or may be prepared from commercially available compounds using standard procedures.

Compounds of formula (X) are either known or may be prepared in accordance with known procedures.

As a further aspect of the invention there is thus provided a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use as a pharmaceutical, particularly in the treatment of patients with diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

According to another aspect of the invention, there is provided the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of patients with diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with diseases characterised by elevated β-amyloid levels or β-amyloid deposits, which method comprises administering to said human or animal subject an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

As a further aspect of the invention there is thus provided a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

The compounds according to the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions for use in the therapy of diseases characterised by elevated β-amyloid levels or β-amyloid deposits, comprising a compound of formula (I) or

a physiologically acceptable salt or solvate thereof together, if desirable, with one or more physiologically acceptable diluents or carriers.

It will be appreciated that diseases characterised by elevated β-amyloid levels or β-amyloid deposits include Alzheimer's disease, mild cognitive impairment, Down's syndrome, hereditary cerebral haemorrhage with β-amyloidosis of the Dutch type, cerebral β-amyloid angiopathy and various types of degenerative dementias, such as those associated with Parkinson's disease, progressive supranuclear palsy, cortical basal degeneration and diffuse Lewis body type of Alzheimer's disease.

Most preferably, the disease characterised by elevated β-amyloid levels or β-amyloid deposits is Alzheimer's disease.

There is also provided a process for preparing such a pharmaceutical formulation which comprises mixing the ingredients.

Compounds of formula (I) may be used in combination with other therapeutic agents. Suitable examples of such other therapeutic agents may be acetylcholine esterase inhibitors (such as tetrahydroaminoacridine, donepezil hydrochloride and rivastigmine), gamma secretase inhibitors, anti-inflammatory agents (such as cyclooxygenase II inhibitors), antioxidants (such as Vitamin E and ginkolidesor), statins or p-glycoprotein (P-gp) inhibitors (such as cyclosporin A, verapamil, tamoxifen, quinidine, Vitamin E-TGPS, ritonavir, megestrol acetate, progesterone, rapamycin, 10,11-methanodibenzosuberane, phenothiazines, acridine derivatives such as GF120918, FK506, VX-710, LY335979, PSC-833, GF-102 and 918).

When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

The compounds according to the invention may, for example, be formulated for oral, inhaled, intranasal, buccal, enteral, parenteral, topical, sublingual, intrathecal or rectal administration, preferably for oral administration.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch, cellulose or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example,

aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl p- hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.
For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds according to the invention may also be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multi-dose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or tonicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

When the compounds of the invention are administered topically they may be presented as a cream, ointment or patch.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 3000 mg; and such unit doses may be administered more than once a day, for example one, two, three or four times per day (preferably once or twice); and such therapy may extend for a number of weeks, months or years.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Examples

Preparation of Intermediates

Description F1

((S)-1-Cyclohexylcarbamoyl-ethyl)-carbamic acid *tert*-butyl ester (F1)

(S)-2-*tert*-Butoxycarbonylamino-propionic acid (1.5 g, 8.0 mmol, 1 equiv), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (1.84 g, 9.6 mmol, 1.2 equiv), 1-hydroxybenzotriazole hydrate (1.47 g, 9.6 mmol, 1.2 equiv), 4-ethylmorpholine (1.76 g, 16 mmol, 2 equiv) and cyclohexylamine (1.1 ml, 9.6 mmol, 1.2 equiv) in CH_2Cl_2 (10 ml) were stirred at room temperature for 16 h. The solution was concentrated *in vacuo* and the residue dissolved in AcOEt. The organic phase was washed with 2N aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give ((S)-1-cyclohexylcarbamoyl-ethyl)-carbamic acid *tert*-butyl ester (F1) (2.2 g, 98%) as a colourless oil.

Description F2

2-(3-Methoxy-phenyl)-2-methyl-propionic acid ethyl ester (F2)

To a solution of (3-methoxy-phenyl)-acetic acid ethyl ester (19.72 g, 0,101 m, 1 equiv) in THF (200 ml) was added NaH (60% in mineral oil, 8.8g, 0.222 mol, 2.2 equiv) then iodomethane (26 ml, 0.4 mol, 4 equiv). The resulting mixture was stirred at room temperature for 16 h then partitioned between AcOEt and saturated $NaHCO_3$ aqueous solution. The two layers were separated and the organic phase washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 2-(3-methoxy-phenyl)-2-methyl-propionic acid ethyl ester (F2) (20.85 g, 98%) as an orange oil.

Description F3

2-(3-Methoxy-phenyl)-2-methyl-propionic acid (F3)

To a solution of 2-(3-methoxy-phenyl)-2-methyl-propionic acid ethyl ester (F2) (20.95g, 94 mmol, 1 equiv) in EtOH (200 ml) was added 2N NaOH aqueous solution (90 ml, 180 mmol, 1.9 equiv) and the resulting mixture was stirred at 70°C for 16 h then cooled to room temperature. Most of EtOH was removed *in vacuo* and the residue extracted with AcOEt then acidified to pH 1. The aqueous phase was then extracted with AcOEt and the organic phase dried over $MgSO_4$ and concentrated *in vacuo* to give 2-(3-methoxy-phenyl)-2-methyl-propionic acid (F3) (15g, 82%) as a yellow oil.

Description F4

[1-(3-Methoxy-phenyl)-1-methyl-ethyl]-carbamic acid benzyl ester (F4)

To a solution of 2-(3-methoxy-phenyl)-2-methyl-propionic acid (F3) (1g, 5.15 mmol, 1 equiv) in toluene (20 ml) at room temperature was added NEt_3 (1.07 ml, 7.72 mmol, 1.5 equiv) and then diphenylphosphoryl azide (2.2 ml, 10.3 mmol, 2 equiv). The resulting mixture was then heated at 80°C for 2 h then benzyl alcohol (1.61 ml, 15.45 mmol, 3 equiv) was added and the solution heated for a further 2 h, cooled to room temperature and partitioned between EtOAc and saturated $NaHCO_3$ aqueous solution. The two layers were separated and the aqueous phase dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 9/1) gave [1-(3-methoxy-phenyl)-1-methyl-ethyl]-carbamic acid benzyl ester (F4) (1g, 65%) as a yellow gum.

Description F5

1-(3-Methoxy-phenyl)-1-methyl-ethylamine (F5)

A flask was charged with [1-(3-methoxy-phenyl)-1-methyl-ethyl]-carbamic acid benzyl ester (F4) (1 g, 3.34 mmol, 1 equiv), 10% palladium on charcoal (50% wet, 100 mg, 10% w/w), NH_4COOH (2.1 g, 33 mmol, 10 equiv), EtOH (40 ml) and H_2O (8 ml). The resulting mixture was stirred at 80°C for 2 h, cooled to room temperature and the catalyst was filtered off using a pad of celite. Most of the EtOH was removed *in vacuo* and the residue was diluted with 1N HCl aqueous solution. The aqueous phase was extracted with AcOEt then basified to pH 13 and extracted twice with AcOEt. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give 1-(3-methoxy-phenyl)-1-methyl-ethylamine (F5) (290 mg, 53%) as a yellow gum.

Description F6

(S)-2-Amino-*N*-cyclohexyl-propionamide (F6)

((S)-1-Cyclohexylcarbamoyl-ethyl)-carbamic acid *tert*-butyl ester (F1) (2.32 g, 8.6 mmol, 1 equiv) was dissolved in 4M HCl in dioxan (40 ml) and the solution was stirred for 1 h at room temperature then concentrated *in vacuo*. The residue was triturated with Et_2O to give (S)-2-amino-*N*-cyclohexyl-propionamide hydrochloride salt (F6) (2.0 g, 95%) as a white solid.

Description F7

5-Nitro-isophthalamic acid methyl ester (F7)

A suspension of 5-nitro-isophthalic acid monomethyl ester (10 g, 44 mmol, 1 equiv) in CH_2Cl_2 (250 ml) was treated with $(COCl)_2$ (4.36 ml, 50 mmol, 1.1 equiv) followed by a few drops of DMF. The resulting mixture was stirred for 30 min at 35°C then cooled to 0°C. 32% aqueous ammonia (10 ml, excess) was slowly added and the resulting mixture was stirred for 5 min. The precipitate formed was filtered to give 5-nitro-isophthalamic acid methyl ester (F7) (9 g, 90%) as a white solid.

Description F8

3-Cyano-5-nitro-benzoic acid methyl ester (F8)

A suspension of 5-nitro-isophthalamic acid methyl ester (F7) (500 mg, 2.23 mmol, 1 equiv) in CH_2Cl_2 (100 ml) was treated with NEt_3 (1.2 g, 12.0 mmol, 5.4 equiv) and trifluoroacetic anhydride (1.4 mg, 6.7 mmol, 3 equiv). The resulting mixture was stirred for 3 h at room temperature then washed with 2N aqueous HCl solution (50 ml), saturated aqueous $NaHCO_3$ solution (50 ml), dried over $MgSO_4$. and concentrated *in vacuo*. The residue was triturated with AcOEt and *iso*-hexane to give 3-cyano-5-nitro-benzoic acid methyl ester (F8) (250 mg, 54%) as a white solid.

Description F9

3-Amino-5-cyano-benzoic acid methyl ester (F9)

To a solution of 3-cyano-5-nitro-benzoic acid methyl ester (F8) (700 mg, 3.39 mmol, 1 equiv) in EtOH (50 ml) was added $SnCl_2$ (3.2 g, 17 mmol, 5 equiv). The resulting mixture was stirred at reflux for 2 h, cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between ice-cold AcOEt and H_2O. The aqueous phase was basified with 2N aqueous NaOH solution until a white precipitate appeared, then slowly with 12.5N aqueous NaOH solution until this precipitate disappeared. The temperature was kept below 10°C during this addition. The two layers were separated and the aqueous phase extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-amino-5-cyano-benzoic acid methyl ester (F9) (300 mg, 50%) as a light tan solid.

Description F10

5-Nitro-*N,N*-dipropyl-isophthalamic acid methyl ester (F10)

A suspension of 5-nitro-isophthalic acid monomethyl ester (1.0 g, 4.44 mmol, 1 equiv) in CH_2Cl_2 (40 ml) was treated with $(COCl)_2$ (655 mg, 5.2 mmol, 1.2 equiv) followed by a few drops of DMF. The resulting mixture was stirred for 1 h at room temperature and then dipropylamine (1.65 g, 15 mmol, 3.4 equiv) was added and the resulting solution stirred for a further 30 min. The solution was then washed with 2N aqueous HCl solution (50 ml), saturated aqueous $NaHCO_3$ solution (50 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 5-nitro-*N,N*-dipropyl-isophthalamic acid methyl ester (F10) (1.5 g, 110%) as a pale yellow oil.

Description F11

5-Amino- *N,N*-dipropyl-isophthalamic acid methyl ester (F11)

A mixture of 5-nitro-*N,N*-dipropyl-isophthalamic acid methyl ester (F10) (1.5 g, 4.9 mmol, 1 equiv), NH_4COOH (3.0 g, 49 mmol, 10 equiv), 10% Pd on charcoal (50% wet, 250 mg, 0.082 equiv w/w), EtOH (20 ml) and H_2O (10 ml) was heated at 50°C for 90 min. The mixture was cooled to room temperature, filtered through a pad of celite and concentrated *in vacuo*. The residue was dissolved in AcOEt (200 ml) and the resulting solution was washed with saturated $NaHCO_3$ solution (100ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 5-amino-*N,N*-dipropyl-isophthalamic acid methyl ester (F11) (1.2 g, 88%) as a white waxy solid.

Description F12

3-Cyclopent-1-enyl-5-(methanesulfonyl-phenyl-amino)-benzoic *tert* butyl ester; 3-cyclopent-2-enyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert* butyl ester; 3-cyclopent-3-enyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert* butyl ester (F12)

To a solution of 3-bromo-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (C44) (1 g, 2.35 mmol, 1 equiv) in DMF (10 ml) was added cyclopentene (415 µl, 4.7 mmol, 2 equiv), palladium(II)acetate (25 mg, 0.10 mmol, 0.05 equiv), tri(*o*-tolyl)phosphine (70 mg, 0.23 mmol, 0.1 equiv) and triethylamine (980 µl, 7 mmol, 3 equiv). The resulting mixture was stirred at 125°C for 16 h then cooled to room temperature and partitioned between H_2O and Et_2O. The two layers were separated and the organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by flash chromatography (*iso*-hexane/AcOEt : 4/1) gave a mixture of 3-cyclopent-1-enyl-5-(methanesulfonyl-phenyl-amino)-benzoic *tert*-butyl ester, 3-cyclopent-2-enyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester and 3-cyclopent-3-enyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (F12) (450 mg , 46%) as a colourless oil.

Description F13

3-Cyclohex-1-enyl-5-(methanesulfonyl-phenyl-amino)-benzoic *tert* butyl ester; 3-cyclohex-2-enyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert* butyl ester; 3-cyclohex-3-enyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert* butyl ester (F13)

Description F13 was prepared in an analogous manner to the procedure described for Description F12 using cyclohexene instead of cyclopentene (470 µl, 4.7 mmol, 2 equiv) and using 3-bromo-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (C44) (1 g, 2.35 mmol, 1 equiv) which yielded 350 mg (40%) of a mixture of 3-cyclohex-1-enyl-5-(methanesulfonyl-phenyl-amino)-benzoic *tert* butyl ester, 3-cyclohex-2-enyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert* butyl ester and 3-cyclohex-3-enyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert* butyl ester (F13) after purification by flash chromatography on silica gel (*iso*-hexane/EtOAc : 5/1)

Description F14

3-(Methanesulfonyl-phenyl-amino)-5-(2-methyl-propenyl)-benzoic acid *tert*-butyl ester (F14)

To a solution of 3-bromo-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (C44) (300 mg, 0.7 mmol, 1 equiv) in DME (7 ml) and H_2O (2 ml) was added tetrakis(triphenylphosphine)-palladium(0) (40 mg, 0.035 mmol, 0.05 equiv), and the suspension was stirred for 30 min. 2,4,6 Triisobutenylcyclotriboroxane-pyridine complex (obtained as described by F. Kerins and D. F. O' Shea in *J. Org. Chem*, **2002**, *67*, 4968-

4971) (466 mg, 0.7 mmol, 1 equiv) and K_2CO_3 (97 mg, 0.7 mmol, 1 equiv) were added and the resulting mixture was stirred at 90°C for 4 h, cooled to room temperature and diluted with AcOEt. The organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (iso-hexane/AcOEt : 4/1) gave 3-(methanesulfonyl-phenyl-amino)-5-(2-methyl-propenyl)-benzoic acid *tert*-butyl ester (F14) (250 mg, 89%) as a pale yellow oil.

Description F15

3-(Hydroxy-methyl-but-1-ynyl)-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (F15)

To a solution of 3-bromo-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (C44) (200 mg, 0.47 mmol, 1 equiv) in DME (2 ml) and H_2O (2 ml) were added K_2CO_3 (136 mg, 1.18 mmol, 2.5 equiv), CuI (9 mg, 0.05 mmol, 0.1 equiv), triphenyl phosphine (14 mg, 0.05 mmol, 0.1 equiv), 10% palladium on charcoal (14 mg, 0.013 mmol, 0.028 equiv) and the solution was stirred at room temperature for 15 min. 2-Methyl-3-butyne-2-ol (113 µl, 1.15 mmol, 2.5 equiv) was added and the resulting mixture was stirred at 90°C for 16 h then cooled to room temperature. The catalyst was removed by filtration through a pad of celite and the filtrate was diluted with AcOEt. The organic phase was washed with 2N aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*iso*-hexane/AcOEt : 2/1) gave 3-(hydroxy-methyl-but-1-ynyl)-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (F15) (150 mg, 75%) as a colourless oil .

Description F16

3-Amino-5-nitro-benzoic acid methyl ester (F16)

To a solution of 3-amino-5-nitro-benzoic acid (65 g, 357 mmol, 1 equiv) in MeOH (650 ml) at 0°C was added $SOCl_2$ dropwise (39 ml, 536 mmol, 1.5 equiv). The resulting solution was allowed to warm to room temperature and stirred for 16 h. A further portion of $SOCl_2$ (10 ml, 137 mmol, 0.4 equiv) was added dropwise and the solution was stirred at room temperature for 5 h, at 50°C for 2 h and then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. The solid residue was triturated with AcOEt/*iso*-hexane to give 3-amino-5-nitro-benzoic acid methyl ester (F16) (55 g, 78%) as a pale yellow solid.

Description F17

3-(4-Chloro-butanoylamino)-5-nitro-benzoic acid methyl ester (F17)

To a solution of 3-amino-5-nitro-benzoic acid methyl ester (F16) (38 g, 194 mmol, 1 equiv) in CH_2Cl_2 (350 ml) was added NEt_3 (32 ml, 230 mmol, 1.2 equiv) followed by 4-chlorobutyryl chloride (24.7 ml, 220 mmol, 1.13 equiv) dropwise over 20 min. The resulting mixture was allowed to warm to room temperature and stirred for 30 min. The organic phase was then washed with 2N aqueous HCl solution, dried over $MgSO_4$ and

concentrated *in vacuo*. The residue was triturated with *iso*-hexane and Et_2O to give 3-(4-chloro-butanoylamino)-5-nitro-benzoic acid methyl ester (F17) (56 g, 96%) as a brown solid.

Description F18

3-Nitro-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (F18)

To a solution of 3-(4-chloro-butanoylamino)-5-nitro-benzoic acid methyl ester (F17) (56 g, 186 mmol, 1 equiv) in THF (500 ml) under nitrogen was added portionwise NaH (60% w/w in mineral oil, 8 g, 200 mmol, 1.07 equiv) over 10 min. The resulting mixture was stirred at room temperature for 1 h then cooled to 0°C and MeOH was added dropwise until bubbling ceased. The solution was concentrated *in vacuo* and the residue diluted with AcOEt. The organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with *iso*-hexane to give 3-nitro-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (F18) (38.5 g, 78%) as a light tan solid.

Description F19

3-Amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (F19)

A flask was charged with 3-nitro-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (F18) (5 g, 19 mmol, 1 equiv), 10% palladium on charcoal (50% wet, 750 mg, 7.5% w/w), NH_4COOH (11.9 g, 190 mmol, 10 equiv) H_2O (30 ml) and MeOH (60 ml). The resulting mixture was stirred at 50°C for 1.5 h, cooled to room temperature and the catalyst was filtered off through a pad of celite. Most of the MeOH was removed *in vacuo* and the residue diluted with saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted twice with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give an off white solid. The catalyst was then washed three times with DMF and the combined organic phases concentrated *in vacuo*. The residue was combined with the material obtained previously and was triturated with Et_2O to give amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (F19) (3.9 g, 88%) as a white solid which was used in the next step without further purification.

Description F20

3-(3-Chloro-propane-1-sulfonylamino)-5-nitro-benzoic acid methyl ester (F20)

To a solution of 3-amino-5-nitro-benzoic acid methyl ester (F16) (45 g, 229 mmol, 1 equiv) in CH_2Cl_2 (450 ml) was added pyridine (18.5 ml, 229 mmol, 1 equiv), DMAP (100 mg, 0.8 mmol, catalytic) and 3-chloropropanesulfonyl chloride (28 ml, 230 mmol, 1 equiv). The resulting mixture was stirred for 40 h then diluted with AcOEt. The organic phase was diluted with 2N aqueous HCl solution. The resulting solid was filtered to give 3-(3-chloro-propane-1-sulfonylamino)-5-nitro-benzoic acid methyl ester (23 g, 32%). The filtrate was separated and the organic phase was washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with AcOEt and *iso*-hexane to give a further 50 g (65%) of 3-(3-chloro-propane-1-sulfonylamino)-5-nitro-benzoic acid methyl ester (F20) as a pale brown solid.

$[M-H]^-$ = 334.9, RT = 3.11 min

Description F21

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-nitro-benzoic acid methyl ester (F21)

To a solution of 3-(3-chloro-propane-1-sulfonylamino)-5-nitro-benzoic acid methyl ester (F20) (73g, 217 mmol, 1 equiv) in EtOH (600 ml) was added Et_3N (60 ml, 430 mmol, 2 equiv) and the resulting mixture was refluxed for 3 h, cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt, washed with 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with *iso*-hexane and AcOEt to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-nitro-benzoic acid methyl ester (F21) (58 g, 88%) as a pale brown solid. $[M+H+NH_3]^+$ = 318.0, RT = 2.78 min

Description F22

3-Amino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (F22)

A flask was charged with 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-nitro-benzoic acid methyl ester (F21) (25 g, 83 mmol, 1 equiv) and 10% palladium (0) on charcoal (50% wet, 5 g, 10% w/w) and EtOH (500 ml). The resulting suspension was stirred under an atmosphere of hydrogen (atmospheric pressure) for 4 h and the catalyst was filtered off through a pad of celite. The catalyst was washed three times with DMF and the combined organic layers were concentrated *in vacuo*. The residue was dissolved in AcOEt and filtered again through celite in order to remove residual catalyst. The organic phase was concentrated *in vacuo*. The residue was triturated with Et_2O to give 3-amino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (F22) (18 g, 80%) as a pale brown solid. $[M+H]^+$ = 271.0, RT = 2.16 min

Description F23

3-Bromo-5-nitro-benzoic acid (F23)

To a solution of 3-amino-5-nitro-benzoic acid (17.6 g, 96.6 mmol, 1 equiv) in 48% aqueous HBr solution (180 ml) at 0°C was added portionwise $NaNO_2$ (8.67 g, 126 mmol, 1.3 equiv) over 20 min. The temperature was kept below 8°C during this addition. The resulting mixture was then added to a suspension of CuBr (9.7 g, 67.6 mmol, 0.7 equiv) in 48% aqueous HBr solution (50 ml) at 65°C over 40 min. The temperature was kept above 60°C during the addition. The resulting mixture was stirred at 70°C for 45 min, cooled to room temperature and diluted with 1L of water. The aqueous phase was extracted three times with Et_2O. The combined organic layers were washed twice with H_2O, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-bromo-5-nitro-benzoic acid (F23) (21 g, 88%) as a brown solid. $[M-H]^-$ = 245.7, RT = 2.82 min

Description F24

3-Bromo-5-nitro-benzoic acid methyl ester (F24)

3-Bromo-5-nitro-benzoic acid methyl ester (F24) was prepared from 3-bromo-5-nitro-benzoic acid (F23) in accordance with an analogous procedure to that described in F46.

Description F27

3-Amino-5-(methanesulfonyl-phenyl-amino)-benzoic acid methyl ester (F27)

A flask was charged with 3-(methanesulfonyl-phenyl-amino)-5-nitro-benzoic acid methyl ester (F26) (400 mg, 1.14 mmol, 1 equiv), 10% palladium on charcoal (50% wet, 40 mg, 5% w/w), NH_4COOH (718 mg, 11.4 mmol, 10 equiv) H_2O (2 ml) and EtOH (10 ml). The resulting mixture was stirred at 50°C for 2 h, cooled to room temperature and the catalyst was filtered off through a pad of celite. Most of the EtOH was removed *in vacuo* and the residue diluted with H_2O and AcOEt. The layers were separated. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give 3-amino-5-(methanesulfonyl-phenyl-amino)-benzoic acid methyl ester (F27) (330 mg, 90%) as a pale orange solid.

Description F28

5-Ethoxy-isophthalic acid dimethyl ester (F28)

K_2CO_3 (31.6 g, 223 mmol, 2.23 equiv) and iodoethane (17.8 ml, 230 mmol, 2.3 equiv) were added to a solution of 5-hydroxy-isophthalic acid dimethyl ester (21 g, 100 mmol, 1 equiv) in acetone (500 ml) at room temperature. The resulting solution was refluxed for 16 h, then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between H_2O and AcOEt. The aqueous phase was extracted with AcOEt and the combined organic layers were washed with 2N aqueous NaOH solution and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 5-ethoxy-isophthalic acid dimethyl ester (F28) (23 g, 96%) as a white solid. RT = 3.13 min

Description F29

5-Ethoxy-isophthalic acid monomethyl ester (F29)

To a solution of 5-ethoxy-isophthalic acid dimethyl ester (F28) (22 g, 92.4 mmol, 1 equiv) in MeOH (440 ml) was added 1N aqueous NaOH solution (87.8 ml, 87.8 mmol, 0.95 equiv) and the resulting solution was stirred at room temperature for 17 h. Most of the MeOH was removed *in vacuo* and the residue was partitioned between AcOEt and 1N aqueous NaOH solution. The aqueous layer was extracted with AcOEt, acidified to pH 1 and re-extracted with AcOEt. The second organic extract was dried over $MgSO_4$ and concentrated *in vacuo* to give 5-ethoxy-isophthalic acid monomethyl ester (F29) (17 g, 82%) as a white solid. $[M+H+NH_3]^+$ = 242.0, RT = 2.79 min

Description F30

3-Benzyloxycarbonylamino-5-ethoxy-benzoic acid methyl ester (F30)

NEt_3 (14.2 ml, 102 mmol, 1.3 equiv) and diphenylphosphoryl azide (22 ml, 102 mmol, 1.3 equiv) were added to a suspension of 5-ethoxy-isophthalic acid monomethyl ester (F29) (17.6 g, 78.6 mmol, 1 equiv) in toluene (250 ml) and the mixture heated at 80°C for 3 h. Benzyl alcohol (12 ml, 118 mmol, 1.5 equiv) was added and the resulting mixture was

refluxed for 4 h, cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt (300 ml) and the resulting solution was washed with 2N aqueous HCl solution (100 ml) followed by saturated aqueous $NaHCO_3$ solution (100 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give 3-benzyloxycarbonylamino-5-ethoxy-benzoic acid methyl ester (F30) (15 g, 62%) as a white solid. $[M-H]^-$ = 328.1 ,RT = 3.46 min

Description F31

3-Amino-5-ethoxy-benzoic acid methyl ester (F31)

A mixture of 3-benzyloxycarbonylamino-5-ethoxy-benzoic acid methyl ester (F30) (15 g, 45.5 mmol, 1 equiv), 10% palladium on charcoal (50% wet, 1.5 g, 5% w/w) and NH_4COOH (15 g, 455 mmol, 10 equiv) H_2O (50 ml) and MeOH (200 ml) was stirred at 50°C for 2h. The mixture was cooled to room temperature and the catalyst was filtered off through a pad of celite. Most of the MeOH was removed *in vacuo* and the residue was partitioned between saturated aqueous $NaHCO_3$ solution and AcOEt. The aqueous phase was re-extracted with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give 3-amino-5-ethoxy-benzoic acid methyl ester (F31) (8.8 g, 99%) as a pale green solid. $[M+H]^+$ = 196.1, RT = 2.49 min

Description F32

5-Dimethylthiocarbamoyloxy-isophthalic acid dimethyl ester (F32)

To a solution of 5-hydroxy-isophthalic acid dimethyl ester (21 g, 100 mmol, 1 equiv) in DMF (300 ml) at room temperature was added DABCO (14.6 g, 130 mmol, 1.3 equiv) followed by dimethylthiocarbamoyl chloride (14.8 g, 120 mmol, 1.2 equiv). The resulting mixture was stirred at room temperature for 16 h and at 60°C for 2 h, then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and H_2O and the aqueous phase re-extracted with AcOEt. The combined organic solution was washed sequentially with 5% aqueous citric acid solution, 2N aqueous NaOH solution and brine, then dried over $MgSO_4$ and concentrated *in vacuo* to give 5-dimethylthiocarbamoyloxy-isophthalic acid dimethyl ester (F32) (23.5 g, 79%) as a pale yellow oil. $[M+H]^+$ = 298.0, RT = 3.06 min

Description F33

5-Dimethylcarbamoylsulfanyl-isophthalic acid dimethyl ester (F33)

5-Dimethylthiocarbamoyloxy-isophthalic acid dimethyl ester (F32) (15.5 g, 52.2 mmol, 1 equiv) was stirred at 200°C for 24 h under nitrogen then cooled to room temperature. Purification by flash chromatography on silica gel (*iso*-hexane/AcOEt : 4/1 then 3/1) gave 5-dimethylcarbamoylsulfanyl-isophthalic acid dimethyl ester (F33) (7.0 g, 45%) and recovered 5-dimethylthiocarbamoyloxy-isophthalic acid dimethyl ester (F32) (2.77 g, 18%), both as white solids. $[M+H]^+$ = 298.0, RT = 2.92 min

Description F34

5-Dimethylcarbamoylsulfanyl-isophthalic acid monomethyl ester (F34)

To a solution of 5-dimethylcarbamoylsulfanyl-isophthalic acid dimethyl ester (F33) (6 g, 20.2 mmol, 1 equiv) in THF (100 ml) at room temperature was added 2N aqueous NaOH solution (9.6 ml, 19.2 mmol, 0.95 equiv). The resulting mixture was stirred for 11 h and then partitioned between AcOEt and H_2O. The two layers were separated and the aqueous phase extracted with AcOEt. After acidification to pH 1, the aqueous phase was extracted twice with AcOEt. The organic solution was dried over $MgSO_4$ then concentrated *in vacuo* to give 5-dimethylcarbamoylsulfanyl-isophthalic acid monomethyl ester (F34) (4.54 g, 79%) as a white solid.

Description F35

***tert*-Butoxycarbonylamino-dimethylcarbamoylsulfanyl-benzoic acid methyl ester (F35)**

To a solution of 5-dimethylcarbamoylsulfanyl-isophthalic acid monomethyl ester (F34) (4.56 g, 16.1 mmol, 1 equiv) in toluene (100 ml) was added triethylamine (6.7 ml, 48 mmol, 3 equiv) and diphenylphosphoryl azide (5.2 ml, 24 mmol, 1.5 equiv). The resulting mixture was stirred under nitrogen at 80°C for 3 h and then *tert*-butanol (4.6 ml, 48 mmol, 3 equiv) was added. The solution was stirred at 80°C for another 16 h then cooled to room temperature and concentrated *in vacuo*. The crude product was dissolved in AcOEt and the resulting solution washed sequentially with 2N aqueous NaOH solution, 2N aqueous HCl solution and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*iso*-hexane/AcOEt : 3/1 to 6/4) gave *tert*-butoxycarbonylamino-dimethylcarbamoylsulfanyl-benzoic acid methyl ester (F35) (2.24 g, 40%). as a white solid.

Description F36

3-*tert*-Butoxycarbonylamino-5-mercapto-benzoic acid (F36)

To a solution of *tert*-butoxycarbonylamino-dimethylcarbamoylsulfanyl-benzoic acid methyl ester (F35) (2.24 g, 6.3 mmol, 1 equiv) in MeOH (30 ml) and H_2O (23 ml) was added 2N aqueous NaOH solution (7 ml, 14mmol, 2.2 equiv). The resulting mixture was refluxed for 3 h and then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and 1N aqueous NaOH solution. The aqueous phase was acidified to pH 1 and extracted twice with AcOEt. The combined organic solutions were dried over $MgSO_4$ then concentrated *in vacuo* to give 3-*tert*-butoxycarbonylamino-5-mercapto-benzoic acid (F36) (1.54 g, 90%) as a white solid.

Description F37

3-*tert*-Butoxycarbonylamino-5-methylsulfanyl-benzoic acid methyl ester (F37)

To a solution of 3-*tert*-butoxycarbonylamino-5-mercapto-benzoic acid (F36) (0.68 g, 2.52 mmol, 1 equiv) in acetone (15 ml) was added K_2CO_3 (3.5 g, 25.3 mmol, 10 equiv) and iodomethane (473 µl, 7.59 mmol, 3 equiv). The resulting mixture was stirred at 50°C for 2 h, cooled to room temperature and concentrated *in vacuo*. The residue was partitioned

between AcOEt and H_2O. The organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*iso*-hexane/AcOEt : 85/15) gave 3-*tert*-butoxycarbonylamino-5-methylsulfanyl-benzoic acid methyl ester (F37) (0.47 g, 63%) as a white solid. $[M-H]^-$ = 296.1, RT = 3.51 min

Description F38

3-*tert*-Butoxycarbonylamino-5-ethylsulfanyl-benzoic acid ethyl ester (F38)

Description F38 was prepared in an analogous manner to that described for Description F37, using iodoethane as the alkylating agent, from 0.68 g (2.53 mmol) of 3-*tert*-butoxycarbonylamino-5-methylsulfanyl-benzoic acid methyl ester (F36), which yielded 3-*tert*-butoxycarbonylamino-5-ethylsulfanyl-benzoic acid ethyl ester (F38) (0.58 g, 71%) as a white solid. $[M-H]^-$ = 324.2, RT = 3.79 min

Description F39

3-Amino-5-methylsulfanyl-benzoic acid methyl ester hydrochloride (F39)

3-*tert*-Butoxycarbonylamino-5-methylsulfanyl-benzoic acid methyl ester (F37) (0.54 g, 1.82 mmol, 1 equiv) was dissolved in dioxan (2 ml) and 4M HCl in dioxan (16 mmol, 4 ml, 8.8 equiv) was added. The solution was stirred at room temperature for 2 h allowing the hydrochloride salt of the amine to precipitate. This precipitate was filtered off, washed with Et_2O and dried giving 3-amino-5-methylsulfanyl-benzoic acid methyl ester hydrochloride (F39) (0.224 g, 52%).

$[M+H]^+$ = 198.1

RT = 2.68 min

Description F40

3-Amino-5-ethylsulfanyl-benzoic acid ethyl ester hydrochloride (F40)

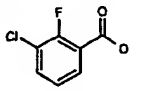
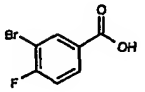
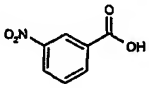
F40 was prepared in an analogous manner to Intermediate 39 from 0.57 g (1.75 mmol) 3-*tert*-butoxycarbonylamino-5-ethylsulfanyl-benzoic acid ethyl (F38) which yielded F40 as a white solid; 0.335 g (73%). $[M+H]^+$ = 226.1, RT = 3.13 min

Description F41

3-Bromo-5-iodo-benzoic acid *tert*-butyl ester (F41)

To a solution of 3-bromo-5-iodo-benzoic acid (50 g, 153 mmol, 1 equiv) in CH_2Cl_2 (500 ml) was added 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (30.8 g, 160 mmol, 1.05 equiv), DMAP (14 g, 114 mmol, 0.75 equiv) and *tert*-butanol (90 ml, 917 mmol, 6 equiv). The resulting mixture was stirred at room temperature for 48 h. DMAP (4.67 g, 38 mmol, 0.25 equiv) was then added and the solution was stirred for another 24 h then concentrated *in vacuo*. The residue was dissolved in AcOEt and washed sequentially with 2N aqueous HCl solution, 1N aqueous NaOH solution and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-bromo-5-iodo-benzoic acid *tert*-butyl ester (F41) (50.6 g, 86%) as a brown solid.

The following compounds were made in an analogous manner to that described for Description F41:

Description	Starting Material
3-Chloro-2-fluoro-benzoic acid *tert*-butyl ester (F42)	
3-Bromo-4-fluoro-benzoic acid *tert*-butyl ester (F43)	
3-Nitro benzoic acid *tert*-butyl ester (F44)	

Description F45

3-Amino-benzoic acid *tert*-butyl ester (F45)

To a solution of 3-nitro-benzoic acid *tert*-butyl ester (F44) (1 g, 4.5 mmol, 1 equiv) in EtOH (30 ml) and H_2O (6 ml) was added 10% palladium on charcoal (50% wet, 100 mg, 5% w/w) and NH_4COOH (2.8 g, 45 mmol, 10 equiv). The resulting mixture was stirred at 50°C for 2h then cooled to room temperature. The catalyst was removed by filtration over a pad of celite. Most of the EtOH was removed *in vacuo* and the residue dissolved in AcOEt. The organic phase was washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-amino-benzoic acid *tert*-butyl ester (F45) (796 mg, 92%) as a colorless oil.

Description F46

3-Amino-4-chloro-benzoic acid methyl ester (F46)

To a solution of 3-amino-4-chloro-benzoic acid (1.7 g, 10 mmol, 1 equiv) in MeOH (70 ml) at 0°C was added $SOCl_2$ (1.46 ml, 20 mmol, 2 equiv). The resulting solution was refluxed for 16 h, cooled to room temperature and concentrated *in vacuo*. The residue was diluted with AcOEt and washed twice with 2N aqueous NaOH solution then brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-amino-4-chloro-benzoic acid methyl ester (F46) (1.8 g, 97%) as a pale yellow oil.

Description F47

4-((Z/E)-But-2-enylamino)-3,5-diiodo-benzoic acid ethyl ester (F47)

To a solution of 4-amino-3,5-diiodo-benzoic acid ethyl ester (commercially available from Maybridge) (72.6 g, 0.17 mmol, 1 equiv) in DMF (450 ml) at 0°C under nitrogen was added NaH (60% in mineral oil, 7.3 g, 0.18 mmol, 1.05 equiv) portionwise over 2 min. After 10 min crotyl bromide (21.5 ml, 0.21 mmol, 1.2 equiv) in DMF (50 ml) was added *via cannula* over 5 min and the resulting mixture was allowed to warm to room temperature over 30 min. 5 ml of EtOH were added and the mixture was concentrated *in*

vacuo. The residue was dissolved in AcOEt and the organic phase was washed with H_2O. The aqueous phase was extracted with AcOEt and the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound (F47) (82 g, 100%) as a pink solid which was used in the next step without further purification. $[M+H]^+ = 472.0$, RT = 4.93 min.

Description F48

3-Ethyl-7-iodo-1 *H*-indole-5-carboxylic acid ethyl ester (F48)

To a solution of 4-((Z/E)-but-2-enylamino)-3,5-diiodo-benzoic acid ethyl ester (F47) (15 g, 31.8 mmol, 1 equiv) in DMF (150 ml) at room temperature under nitrogen were added $Pd(OAc)_2$ (357 mg, 1.6 mmol, 0.05 equiv), NaCOOH (6.5 g, 95.6 mmol, 3 equiv), Na_2CO_3 (8.4 g, 79.6 mmol, 2.5 equiv) and Nbu_4Cl (8.0 g, 35.0 mmol, 1.1 equiv). The resulting suspension was stirred under nitrogen at 80°C for 30 min then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and H_2O and the two phases were separated. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 9/1) gave the title compound (F48) (6.3 g, 58%) as a white solid. $[M+H]^+ = 344.0$, RT = 3.86 min.

Description F49

7-Benzyloxycarbonylamino-3-ethyl-1 *H*-indole-5-carboxylic acid ethyl ester (F49)

To a solution of 3-ethyl-7-iodo-1 *H*-indole-5-carboxylic acid ethyl ester (F48) (850 mg, 2.48 mmol, 1 equiv) in toluene (20 ml) at room temperature under nitrogen were added benzyl carbamate (562 mg, 3.72 mmol, 1.5 equiv), copper iodide (24 mg, 0.13 mmol, 0.05 equiv) K_3PO_4 (1.05 g, 4.8 mmol, 2 equiv) and N,N'-dimethylethylenediamine (26 µl, 0.25 mmol, 0.1 equiv) and the resulting suspension was stirred at 100°C for 30 min then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and H_2O and the two phases were separated. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 9/1) gave the title compound (F49) (250 mg, 27%) as an off white solid. $[M+H]^+ = 367.1$, RT = 3.73 min.

Description F50

7-Amino-3-ethyl-1 *H*-indole-5-carboxylic acid ethyl ester (F50)

To a solution of 7-benzyloxycarbonylamino-3-ethyl-1 *H*-indole-5-carboxylic acid ethyl ester (F49) (250 mg, 0.68 mg, 1 equiv) in EtOH (10 ml) were added NH_4COOH (431 mg, 6.8 mmol, 10 equiv), H_2O (2 ml), Pd (10% w/w on charcoal, 50 mg, 0.02 equiv w/w) and the resulting mixture was stirred at 70°C for 1.5 h. Another 200 mg of Pd (10% w/w on charcoal, 0.08 equiv w/w) were then added and the resulting mixture stirred at 70°C for another 30 min then cooled to room temperature. The catalyst was filtered off through a pad of celite and most of the EtOH was removed *in vacuo*. The residue was partitioned between AcOEt and H_2O and the two phases were separated. The organic phase was

dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound (F50) (150 mg, 95%) as an off white solid which was used in the next step without further purification. $[M+H]^+$ = 233.1, RT = 3.19 min.

Description F51

1,1,5-Trimethyl-hexylamine (F51)

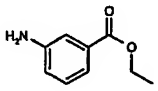
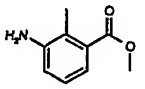
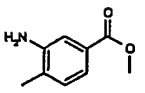
Description F51 was obtained according to S. S. Berg and D. T. Cowling, *J. Chem. Soc.* (C) 1971, 1653-1658.

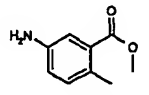
Description 1

3-Methanesulfonylamino-benzoic acid methyl ester (D1)

To a solution of 3-amino-benzoic acid methyl ester (10 g, 66 mmol, 1 equiv) in CH_2Cl_2 (100 ml) at room temperature were added pyridine (5.86 ml, 72.6 mmol, 1.1 equiv), CH_3SO_2Cl (5.37 ml, 70 mmol, 1.06 equiv) and DMAP (1g, 8.2 mmol, 0.12 equiv) and the resulting mixture was stirred at this temperature for 16 h then concentrated *in vacuo*. The residue was diluted with AcOEt and the organic phase was washed with 2N HCl aqueous solution, saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated in vacuo to give 3-methanesulfonylamino-benzoic acid methyl ester (D1) (13.4 g, 89%) as a pale yellow oil. $[M-H]^-$ = 228.0, RT = 2.40 min

The following compounds were prepared in accordance with the procedure described in Description 1 from the appropriate aniline starting material:

Description	Starting Material
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-methanesulfonylamino-benzoic acid methyl ester (D2)	F22
5-Methanesulfonylamino-*N*,*N*-dipropyl-isophthalamic acid methyl ester (D3)	F11
3-Ethoxy-5-methanesulfonylamino-benzoic acid methyl ester (D4)	F31
3-Methanesulfonylamino-benzoic acid ethyl ester (D5)	
3-Methanesulfonylamino-benzoic acid *tert*-butyl ester (D6)	F45
3-Cyano-5-methanesulfonylamino-benzoic acid methyl ester (D7)	F9
3-Methanesulfonylamino-2-methyl-benzoic acid methyl ester (D10)	
3-Methanesulfonylamino-4-methyl-benzoic acid methyl ester (D11)	
4-Chloro-3-methanesulfonylamino-benzoic acid methyl ester	F46

(D12)	
5-Methanesulfonylamino-2-methyl-benzoic acid methyl ester (D13)	
3-Methanesulfonylamino-5-methylsulfanyl-benzoic acid methyl ester (D14)	F39
3-Methanesulfonylamino-5-ethylsulfanyl-benzoic acid methyl ester (D15)	F40
3-Methanesulfonylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D18)	F19
3-Ethyl-7-methanesulfonylamino-1*H*-indole-5-carboxylic acid ethyl ester (D50)	F50

Description 16

5-Methanesulfonylamino-nicotinic acid ethyl ester (D16)

D16 was obtained in an analogous manner to the procedure described in Description 17 from 5-amino-nicotinic acid ethyl ester (which was prepared in accordance with Jensen, H. H. *et al Chem. Europ. J* **2002**, 8 (5), 1218-1226).

Description 17

2-Methanesulfonylamino-isonicotinic acid ethyl ester (D17)

To a solution of 2-amino-isonicotinic acid ethyl ester (obtained according to Seewood, D. L. and all, *J. Med. Chem.* **2001**, 44(1), 78-93) (1 g, 6.02 mmol, 1 equiv) in CH_2Cl_2 (60 ml) at room temperature were added pyridine (700 µl, 8.6 mmol, 1.4 equiv), CH_3SO_2Cl (606 µl, 0.78 mmol, 1.25 equiv) and DMAP (100 mg, 0.82 mmol, 0.13 equiv) and the resulting mixture was stirred at this temperature for 16 h then partitioned between CH_2Cl_2 and $NaHCO_3$ saturated aqueous solution. The two layers were separated and the organic phase was washed water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O and the precipitate filtered off to give 2-methanesulfonylamino-isonicotinic acid ethyl ester (D17) (1.6 g, 110%) as an orange solid.

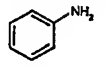
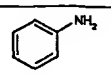
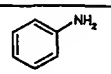
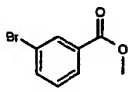
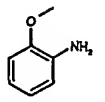
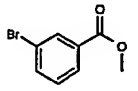
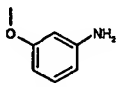
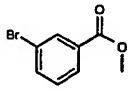
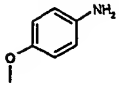
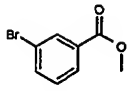
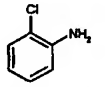
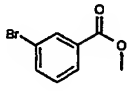
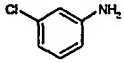
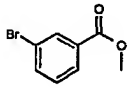
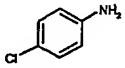
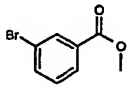
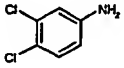
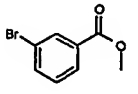
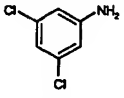
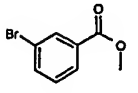
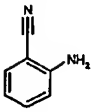
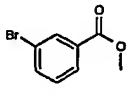
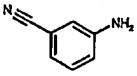
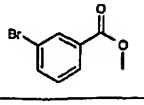
Description 27

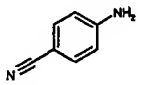
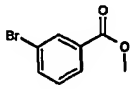
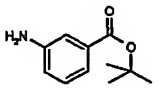
3-(4-Trifluoromethyl-phenylamino)-benzoic acid ethyl ester (D27)

A flask was charged under nitrogen with 4-bromo-trifluoromethyl-benzene (1.25 ml, 8.9 mmol, 1 equiv), Cs_2CO_3 (4.4 g, 13.4 mmol, 1.5 equiv), palladium(II)acetate (101 mg, 0.45 mmol, 0.05 equiv), rac-BINAP (416 mg, 0.67 mmol, 0.075 equiv) and toluene (30 ml). 3-Amino-benzoic acid ethyl ester (1.6 ml, 10.7 mmol, 1.2 equiv) was then added *via syringe* and the resulting mixture was stirred at 100°C for 3 h then cooled to room temperature and diluted with AcOEt. The organic phase was washed with H_2O, 2N HCl aqueous solution then brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification

of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 4/1) gave 3-(4-trifluoromethyl-phenylamino)-benzoic acid ethyl ester (D27) (600 mg, 21%) as an off-white solid.

The following compounds were prepared in an analogous manner to that described for Description 27 from the appropriate aniline and aryl halide:

Description	Aniline	Aryl halide
2-Fluoro-3-phenylamino-benzoic acid *tert*-butyl ester (D31)		F42
4-Fluoro-3-phenylamino-benzoic acid *tert*-butyl ester (D32)		F43
3-Phenylamino-benzoic acid methyl ester (D49)		
3-(2-Methoxy-phenylamino)-benzoic acid methyl ester (D33)		
3-(3-Methoxy-phenylamino)-benzoic acid methyl ester (D34)		
3-(4-Methoxy-phenylamino)-benzoic acid methyl ester (D35)		
3-(2-Chloro-phenylamino)-benzoic acid methyl ester (D36)		
3-(3-Chloro-phenylamino)-benzoic acid methyl ester (D37)		
3-(4-Chloro-phenylamino)-benzoic acid methyl ester (D38)		
3-(3,4-Dichloro-phenylamino)-benzoic acid methyl ester (D39)		
3-(3,5-Dichloro-phenylamino)-benzoic acid methyl ester (D40)		
3-(2-Cyano-phenylamino)-benzoic acid methyl ester (D41)		
3-(3-Cyano-phenylamino)-benzoic acid methyl ester (D42)		

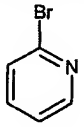
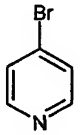
3-(4-Cyano-phenylamino)-benzoic acid methyl ester (D43)		
3-Bromo-5-phenylamino-benzoic acid *tert*-butyl ester (D44)		F41
3-(Naphthalen-1-ylamino)-benzoic acid *tert*-butyl ester (D45)		F45
3-Nitro-5-phenylamino-benzoic acid methyl ester (F25)		F24

Description 47

3-(Pyridin-2-ylamino)-benzoic acid *tert*-butyl ester (D47)

A flask was charged under nitrogen with 3-bromo-pyridine (908 µl , 9.42 mmol, 1 equiv), *t*-BuONa (1.36 g, 14.1 mmol, 1.5 equiv), tris(dibenzylideneacetone)dipalladium(0) (86 mg, 0.09 mmol, 0.01 equiv), 1,3-bis-(2,6-diisopropyl-phenyl)-4,5-dihydro-3*H*-imidazol-1-ium chloride (80 mg, 0.19 mmol, 0.02 equiv) and dioxan (30 ml). 3-Amino-benzoic acid *tert*-butyl ester (2 g, 10.4 mmol, 1.1 equiv) was then added and the resulting mixture was stirred at 100°C for 16 h then cooled to room temperature and diluted with AcOEt. The organic phase was washed with 2N HCl aqueous solution. The aqueous phase was basified to pH 13 with 2N NaOH aqueous solution and extracted twice with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 1/2) gave 3-(pyridin-2-ylamino)-benzoic acid *tert*-butyl ester (D47) (420 mg, 16%) as a pale yellow oil.

The following compounds were obtained in an analogous manner to that described for Description 47 from the appropriate aniline and aryl halide:

Description	Aryl halide	Aniline
3-(Pyridin-2-ylamino)-benzoic acid *tert*-butyl ester (D46)		F45
3-(Pyridin-4-ylamino)-benzoic acid *tert*-butyl ester (D48)		F45

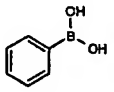
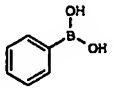
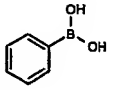
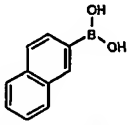
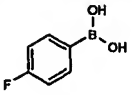
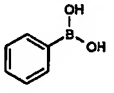
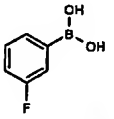
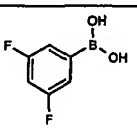
Preparation of Esters

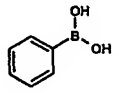
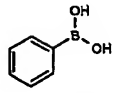
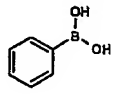
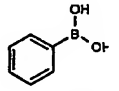
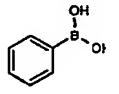
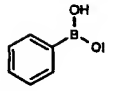
Ester 1

3-(Methanesulfonyl-phenyl-amino)-benzoic acid methyl ester (C1)

To a solution of 3-methanesulfonylamino-benzoic acid methyl ester (D1) (2g, 8.7 mmol, 1 equiv) in CH_2Cl_2 (25 ml) were added phenylboronic acid (2.1g, 17.5 mmol, 2 equiv), $Cu(OAc)_2$ (1.9 g, 10 mmol, 1.15 equiv), NEt_3 (2.4 ml, 17.5 mmol, 2 equiv) and powered activated 4A molecular sieves (1g, 50% w/w). The resulting mixture was stirred at room temperature for 16 h then the molecular sieves were filtered off through a pad of celite and the organic phase was washed with 2N HCl aqueous solution, $NaHCO_3$ saturated aqueous solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 6/1) gave 3-(methanesulfonyl-phenyl-amino)-benzoic acid methyl ester (C1) (680 mg, 26%) as a white solid. $[M+H-SO_2Me]^+$ = 227.0, R.T. = 3.04

The following esters were prepared in an analogous manner to the procedure described for Ester 1 from the corresponding N-aryl sulphonamide and boronic acid starting materials:

Ester	**N-aryl sulfonamide**	**Boronic acid**
3-(Dioxo-1λ^6-isothiazolidin-2-yl)-5-(methanesulfonyl-phenyl-amino)-benzoic acid methyl ester (C2)	D2	
3-(Methanesulfonyl-phenyl-amino)-5-*N*, *N*-dipropyl-isophthalamic acid methyl ester (C3)	D3	
3-Ethoxy-5-(methanesulfonyl-phenyl-amino)-benzoic acid methyl ester (C4)	D4	
3-(Methanesulfonyl-naphthalen-2-yl-amino)-benzoic acid ethyl ester (C5)	D5	
3-[(4-Fluoro-phenyl)-methanesulfonyl-amino]-benzoic acid *tert*-butyl ester (C6)	D6	
Cyano-(methanesulfonyl-phenyl-amino)-benzoic acid methyl ester (C7)	D7	
3-[(3-Fluoro-phenyl)-methanesulfonyl-amino]-benzoic acid *tert*-butyl ester (C8)	D6	
3-[(3,5-Difluoro-phenyl)-methanesulfonyl-amino]-benzoic acid *tert*-butyl ester (C9)	D6	

3-(Methanesulfonyl-phenyl-amino)-2-methyl-benzoic acid methyl ester (C10)	D10	
3-(Methanesulfonyl-phenyl-amino)-4-methyl-benzoic acid methyl ester (C11)	D11	
4-Chloro-3-(methanesulfonyl-phenyl-amino)-benzoic acid methyl ester (C12)	D12	
3-(Methanesulfonyl-phenyl-amino)-5-methyl-benzoic acid methyl ester (C13)	D13	
3-(Methanesulfonyl-phenyl-amino)-5-methylsulfanyl-benzoic acid methyl ester (C14)	D14	
3-(Methanesulfonyl-phenyl-amino)-5-ethylsulfanyl-benzoic acid ethyl ester (C15)	D15	

Ester 16

5-(Methanesulfonyl-phenyl-amino)-nicotinic acid ethyl ester (C16)

Ester 16 was prepared in an analogous manner to Ester 17 from 5-methanesulfonylamino-nicotinic acid ethyl ester (D16).

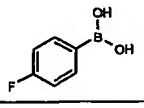
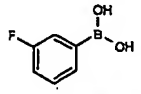
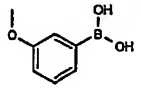
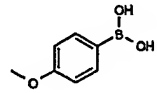
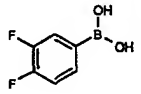
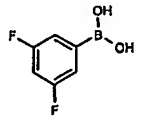
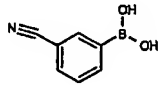
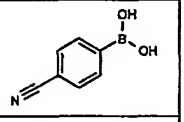
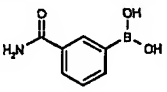
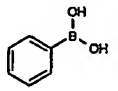
Ester 17

2-(Methanesulfonyl-phenyl-amino)-isonicotinic acid ethyl ester (C17)

To a solution of 2-methanesulfonylamino-isonicotinic acid ethyl ester (D17) (1.47 g, 6.02 mmol, 1 equiv) in CH_2Cl_2 (25 ml) were added phenylboronic acid (2.2g, 18.0 mmol, 3 equiv), $Cu(OAc)_2$ (2.19 g, 12.06 mmol, 2 equiv), NEt_3 (2.5 ml, 18.0 mmol, 3 equiv) and powered activated 4A molecular sieves (1g, 70% w/w). The resulting mixture was stirred at room temperature for 16 h then the molecular sieves were filtered off through a pad of celite and the resulting solution was concentrated *in vacuo*. The residue was partitioned between AcOEt and saturated $NaHCO_3$ aqueous solution and the two layers were separated. the organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 2/1) gave 2-(methanesulfonyl-phenyl-amino)-isonicotinic acid ethyl ester (C17) (394 mg, 21%) as a yellow solid.

The following esters were prepared in an analogous manner to the procedure described for Ester 1 from the corresponding N-aryl sulphonamide and boronic acid starting materials:

Ester	**N-aryl sulfonamide**	**Boronic acid**

3-[(4-Fluoro-phenyl)-methanesulfonyl-amino]-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (C18)	D18	
3-[(3-Fluoro-phenyl)-methanesulfonyl-amino]-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (C19)	D18	
3-[(3-Methoxy-phenyl)-methanesulfonyl-amino]-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (C20)	D18	
3-[(4-Methoxy-phenyl)-methanesulfonyl-amino]-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (C21)	D18	
3-[(3,4-Difluoro-phenyl)-methanesulfonyl-amino]-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (C22)	D18	
3-[(3,5-Difluoro-phenyl)-methanesulfonyl-amino]-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (C23)	D18	
3-[(3-Cyano-phenyl)-methanesulfonyl-amino]-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (C24)	D18	
3-[(4-Cyano-phenyl)-methanesulfonyl-amino]-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (C25)	D18	
3-[(3-Carbamoyl-phenyl)-methanesulfonyl-amino]-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (C26)	D18	
Ethyl-(methanesulfonyl-phenyl-amino)1H-indole-5-carboxylic acid ethyl ester (C59)	D50	

Ester 27

3-[Methanesulfonyl-(4-trifluoromethyl-phenyl)-amino]-benzoic acid ethyl ester (C27)

To a solution of 3-(4-trifluoromethyl-phenylamino)-benzoic acid ethyl ester (D27) (600 mg, 1.94 mmol, 1 equiv) in THF (10 ml) at –78°C was added LDA (2M in THF/*n*-heptane, 2.45 ml, 4.9 mmol, 2.5 equiv) dropwise and the resulting mixture was stirred at this temperature for a further 5 min. Methanesulfonyl chloride (376 µl, 4.9 mmol, 2.5 equiv) was then added dropwise and the resulting mixture was allowed to warm to room

temperature over 30 min then diluted with AcOEt. The organic phase was washed with 2N HCl aqueous solution, 2N NaOH aqueous solution and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 3/1) gave 3-[methanesulfonyl-(4-trifluoromethyl-phenyl)-amino]-benzoic acid ethyl ester (C27) (450 mg, 60%) as a colourless oil.

The following esters were obtained in analogous manner to that described for Ester 27 from the appropriate diphenylamine using the appropriate alkylsulfonyl chloride:

Ester	*N,N*-diarylamine
3-(Ethanesulfonyl-phenyl-amino)-benzoic acid methyl ester (C28)	D49
3-[(Butane-1-sulfonyl)-phenyl-amino]-benzoic acid methyl ester (C29)	D49
3-[Phenyl-(propane-2-sulfonyl)-amino]-benzoic acid methyl ester (C30)	D49
2-Fluoro-3-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (C31)	D31
4-Fluoro-3-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (C32)	D32
3-[Methanesulfonyl-(2-methoxy-phenyl)-amino]-benzoic acid methyl ester (C33)	D33
3-[Methanesulfonyl-(3-methoxy-phenyl)-amino]-benzoic acid methyl ester (C34)	D34
3-[Methanesulfonyl-(4-methoxy-phenyl)-amino]-benzoic acid methyl ester (C35)	D35
3-[Methanesulfonyl-(2-chloro-phenyl)-amino]-benzoic acid methyl ester (C36)	D36
3-[Methanesulfonyl-(3-chloro-phenyl)-amino]-benzoic acid methyl ester (C37)	D37
3-[Methanesulfonyl-(4-chloro-phenyl)-amino]-benzoic acid methyl ester (C38)	D38
3-[Methanesulfonyl-(3,4-dichloro-phenyl)-amino]-benzoic acid methyl ester (C39)	D39
3-[Methanesulfonyl-(3,5-dichloro-phenyl)-amino]-benzoic acid methyl ester (C40)	D40
3-[Methanesulfonyl-(2-cyano-phenyl)-amino]-benzoic acid methyl ester (C41)	D41

3-[Methanesulfonyl-(3-cyano-phenyl)-amino]-benzoic acid methyl ester (C42)	D42
3-[Methanesulfonyl-(4-cyano-phenyl)-amino]-benzoic acid methyl ester (C43)	D43
3-Bromo-5-(methanesulfonyl-phenyl-amino)-benzoic acid dimethyl-ethyl ester (C44)	D44
3-(Methanesulfonyl-naphthalen-1-yl-amino)-benzoic acid *tert*-butyl ester (C45)	D45
3-(Methanesulfonyl-phenyl-amino)-5-nitro-benzoic acid methyl ester (F26)	F25

Ester 47

3-(Methanesulfonyl-pyridin-3-yl-amino)-benzoic acid *tert*-butyl ester (C47)

To a solution of 3-(pyridin-3-ylamino)-benzoic acid *tert*-butyl ester (D47) (420 mg, 1.56 mmol, 1 equiv) in THF (10 ml) at –78°C was added LDA (2M in THF/*n*-heptane, 2.33 ml, 4.67 mmol, 3 equiv) dropwise and the resulting mixture was stirred at this temperature for a further 5 min. Methanesulfonyl chloride (361 µl, 4.9 mmol, 2.5 equiv) was then added dropwise and the resulting mixture was allowed to warm to room temperature over 30 min then diluted with AcOEt. The organic phase was washed with 2N NaOH aqueous solution and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 1/2) gave 3-(methanesulfonyl-pyridin-3-yl-amino)-benzoic acid *tert*-butyl ester (C47) (230 mg, 42%) as a pale yellow oil.

The following esters were obtained using an analogous process to that described for Ester 47 from the appropriate diphenylamine starting material:

Ester	Starting Material
3-(Methanesulfonyl-pyridin-2-yl-amino)-benzoic acid *tert*-butyl ester (C46)	D46
3-(Methanesulfonyl-pyridin-4-yl-amino)-benzoic acid *tert*-butyl ester (C48)	D48

Ester 49

3-Ethylamino-5-(methanesulfonyl-phenyl-amino)-benzoic acid methyl ester (C49)

To a solution of 3-amino-5-(methanesulfonyl-phenyl-amino)-benzoic acid methyl ester (F27) (330 mg, 1.03 mmol, 1 equiv) in $(CH_2Cl)_2$ (10 ml) was added sodium triacetoxyborohydride (306 mg, 1.44 mmol, 1.4 equiv), acetaldehyde (86 µl, 1.44 mmol, 1.4 equiv) and CH_3COOH (71 µl, 1.24 mmol, 1.2 equiv). The resulting mixture was stirred at room temperature for 2 h, diluted with CH_2Cl_2 (20 ml), washed with saturated

aqueous $NaHCO_3$ solution (20 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 1/2) 3-ethylamino-5-(methanesulfonyl-phenyl-amino)-benzoic acid methyl ester (C49) (260 mg, 72%) as a pale yellow solid.

Ester 50

3-(Benzyl-methyl-amino)-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (C50)

A flask was charged under nitrogen with 3-bromo-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (C44) (800 mg ,1.9 mmol, 1 equiv), sodium *tert*-butoxide (274 mg, 2.85 mmol, 1.5 equiv), tris(dibenzylideneacetone)dipalladium(0) (92 mg, 0.1 mmol, 0.05 equiv), 2-(dicyclohexylphosphino)biphenyl (50 mg, 0.14 mmol, 0.075 equiv) and toluene (20 ml). N-Methylbenzylamine (368 µl, 2.85 mmol, 1.5 equiv) was then added *via syringe* and the resulting mixture was stirred at 90°C for 2 h then N-methylbenzylamine (200 µl, 1.54 mmol, 0.8 equiv) was added. After 3 h, the mixture was cooled to room temperature, diluted with H_2O and AcOEt. The layers were separated, the aqueous phase diluted with saturated aqueous $NaHCO_3$ solution and extracted with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 3/1) gave 3-(benzyl-methyl-amino)-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (C50) (600 mg, 68%) as a pale yellow oil.

Ester 51

3-(Methanesulfonyl-phenyl-amino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (C51)

A flask was charged under nitrogen with 3-bromo-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (C44) (1.1 g, 2.58 mmol, 1 equiv), Cs_2CO_3 (1.18 g, 3.61 mmol, 1.4 equiv), tris(dibenzylideneacetone)dipalladium(0) (47 mg, 0.05 mmol, 0.02 equiv), Xantphos (90 mg, 0.15 mmol, 0.06 equiv) and toluene (20 ml). Pyrrolidin-2-one (216 µl, 2.84 mmol, 1.1 equiv) was then added *via syringe* and the resulting mixture was stirred at 100°C for 16 h. Xantphos (30 mg, 0.05 mmol, 0.02 equiv), tris(dibenzylideneacetone)dipalladium(0) (20 mg, 0.021 mmol, 0.085 equiv) and pyrrolidin-2-one (100 µl, 1.31 mmol, 0.5 equiv) were then added and the stirring was continued at 100°C for 16 h. The mixture was then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between H_2O and AcOEt and the aqueous phase re-extracted with AcOEt. The combined organic solutions were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 3/2) gave 3-(methanesulfonyl-phenyl-amino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (C51) (1.0 g, 90%) as a white solid.

Ester 53

3-Ethynyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (C53)

To a solution of 3-(hydroxy-methyl-but-1-ynyl)-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (F15) (600 mg, 1.40 mmol, 1 equiv) in toluene (20 ml) was added NaH (60% dispersion in mineral oil, 60 mg, 1.5 mmol, 1.1 equiv). The resulting mixture was stirred at 110°C for 2 h, cooled to room temperature and diluted with AcOEt. The organic phase was washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-ethynyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (C53) (550 mg, 105%) as a pale brown oil.

Ester 54

(Methanesulfonyl-phenyl-amino)-methyl-biphenyl-3-carboxylic acid dimethyl-ethyl ester (C54)

Ester 54 was prepared according to an analogous procedure described for Ester 55, using (2-methylphenyl)boronic acid instead of 2.6-dimethylphenylboronic acid which yielded (methanesulfonyl-phenyl-amino)-methyl-biphenyl-3-carboxylic acid dimethyl-ethyl ester (C54) (130 mg, 63%) from 3-bromo-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (C44) (200 mg, 0.47 mmol).

Ester 55

(Methanesulfonyl-phenyl-amino)-dimethyl-biphenyl-3-carboxylic acid *tert*-butyl ester (C55)

To a solution of 3-bromo-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (C44) (200 mg, 0.47 mmol, 1 equiv) in toluene (1 ml) and EtOH (1 ml) were added tetrakis(triphenylphosphine)-palladium(0) (54 mg, 0.047 mmol, 0.1 equiv), 2,6-dimethylphenylboronic acid (74 mg, 0.49 mmol, 1.05 equiv) and K_2CO_3 (98 mg, 0.71 mmol, 1.5 equiv) and the resulting mixture was stirred at 90°C for 16 h, cooled to room temperature and diluted with AcOEt. The organic phase was washed with a 2N NaOH aqueous solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*iso*-hexane/AcOEt : 3/1) gave (methanesulfonyl-phenyl-amino)-dimethyl-biphenyl-3-carboxylic acid *tert*-butyl ester (C55) (130 mg, 61%) as a pale yellow oil.

Ester 56

3-Cyclopentyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (C56)

To a solution of 3-cyclopent-1-enyl-5-(methanesulfonyl-phenyl-amino)-benzoic *tert*-butyl ester, 3-cyclopent-2-enyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester and 3-cyclopent-3-enyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (F12) (450 mg, 1.09 mmol, 1 equiv) in EtOH (10 ml) and H_2O (2 ml) was added 10% palladium on charcoal (50% wet, 450 mg, 5% w/w) and NH_4COOH (687 mg, 10.90 mmol, 10 equiv). The resulting mixture was stirred at 50°C for 1h then cooled to room

temperature. The catalyst was removed by filtration over a pad of celite. Most of the EtOH was removed *in vacuo* and the residue dissolved in AcOEt. The organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-cyclopentyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (C56) (420 mg, 92%) as a colorless oil.

The following esters were prepared in an analogous manner to the procedure described for Ester 56:

Ester	Starting Material
3-Cyclohexyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (C57)	F13
3-Isobutyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (C52)	F14

Ester 58

3-(Methanesulfonyl-phenyl-amino)-5-prop-1-ynyl-benzoic acid *tert*-butyl ester (C58)

To a solution of 3-bromo-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (C44) (200 g, 0.47 mmol, 1 equiv) in toluene (10 ml) was added tetrakis(triphenylphosphine)-palladium(0) (16mg, 0.014 mmol, 0.03 equiv) and tributyl-prop-1-ynyl-stannane (171 µl, 0.56 mmol, 1.2 equiv) and the resulting mixture was stirred at 100°C for 16 h then cooled to room temperature and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*iso*-hexane/AcOEt : 17/3) gave 3-(ethanesulfonyl-phenyl-amino)-5-prop-1-ynyl-benzoic acid *tert*-butyl ester (C58) (150 mg, 83%) as a colourless oil.

Preparation of BOC-protected amines

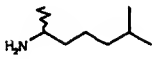
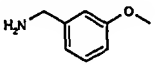
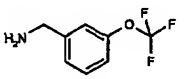
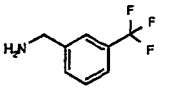
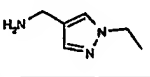
Description G1

((1S,2R)-1-Benzyl-3-cyclohexylamino-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (G1)

((S)-(S)-1-Oxiranyl-2-phenyl-ethyl)-carbamic acid *tert*-butyl ester (10 g, 38 mmol, 1 equiv) [Chirex 1819W94 Lot#9924382] was dissolved in EtOH (100 ml) and cyclohexylamine (13 ml, 114 mmol, 3 equiv) was added. The resulting mixture was heated, under an atmosphere of nitrogen, for 12 h at reflux temperature. The mixture was cooled and the solvent was removed by evaporation *in vacuo*. The resulting white solid was washed with H_2O and then with Et_2O before drying *in vacuo* to give ((1S,2R)-1-benzyl-3-cyclohexylamino-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (G1) (9.0 g, 66%).

$[M+H]^+ = 363.2$

The following Boc-protected amines were prepared in an analogous manner to that described for Description G1 by substituting cyclohexylamine with the starting materials indicated:

Boc-protected Amine	**Starting Material**
[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-carbamic acid *tert*-butyl ester (G2)	F6
[(1S,2R)-1-Benzyl-3-(1,5-dimethyl-hexylamino)-2-hydroxy-propyl]-carbamic acid *tert*-butyl ester (G3)	
[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-carbamic acid *tert*-butyl ester (G4)	
[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethoxy-benzylamino)-propyl]-carbamic acid *tert*-butyl ester (G5)	
[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-carbamic acid tert-butyl ester (G6)	
{(1S,2R)-1-Benzyl-2-hydroxy-3-[1-(3-methoxy-phenyl)-1-methyl-ethylamino]-propyl}-carbamic acid *tert*-butyl ester (G7)	F5
((1S,2R)-1-Benzyl-3-cyclopropylamino-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (G8)	
((1S,2R)-1-Benzyl-3-[(1-ethyl-1*H*-pyrazol-4-ylmethyl]-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (G9)	
[(1S,2R)-1-Benzyl-2-hydroxy-3-(1,1,5-trimethyl-hexylamino)-propyl]- carbamic acid *tert*-butyl ester (G10)	F51

Preparation of Amines

Amine 1

(2R,3S)-3-Amino-1-cyclohexylamino-4-phenyl-butan-2-ol *di*-hydrogen chloride (B1)

((1S,2R)-1-benzyl-3-cyclohexylamino-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (G1) (9 g, 25 mmol, 1 equiv) was dissolved in MeOH (70 ml) and then a 4M solution of HCl in dioxan (60 ml, excess) was added. The resulting mixture was stirred for 3 h at room temperature and then the solvents were removed by evaporation *in vacuo*. The resulting residue was washed with AcOEt and then with Et_2O before drying *in vacuo* to give (2R,3S)-3-amino-1-cyclohexylamino-4-phenyl-butan-2-ol *di*-hydrogen chloride (B1) as a white solid (7.4 g, 88%).

The following amines were prepared in an analogous manner described for Amine 1 substituting the appropriate BOC-protected amines for ((1S,2R)-1-benzyl-3-cyclohexylamino-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester. In some cases the 4M HCl in dioxane was replaced with 3 equivalents of p-toluene sulphonic acid to give the tosic acid salts as the product.

Amine	Starting Material
(S)-2-((2R,3S)-3-Amino-2-hydroxy-4-phenyl-butylamino)-*N*-cyclohexyl-propionamide *di*-hydrogen chloride (B2)	G2
(2R,3S)-3-Amino-1-(1,5-dimethyl-hexylamino)-4-phenyl-butan-2-ol *di*-hydrogen chloride (B3)	G3
(2R,3S)-3-Amino-1-(3-methoxy-benzylamino)-4-phenyl-butan-2-ol (B4)	G4
(2R,3S)-3-Amino-4-phenyl-1-(3-trifluoromethoxy-benzylamino)-butan-2-ol ditosylate (B5)	G5
(2R,3S)-3-Amino-4-phenyl-1-(3-trifluoromethyl-benzylamino)-butan-2-ol ditosylate (B6)	G6
(2R,3S)-3-Amino-1-[1-(3-methoxy-phenyl)-1-methyl-ethylamino]-4-phenyl-butan-2-ol di tosylate (B7)	G7
(2R,3S)-3-Amino-1-*sec*-butylamino-4-phenyl-butan-2-ol *di*-hydrogen chloride (B8)	G8
(2R,3S)-3-Amino-1-[(1-ethyl-1*H*-pyrazol-4-ylmethyl)-amino]-4-phenyl-butane-2-ol di tosylate (B9)	G9
(2R,3S)-3-Amino—4-phenyl-1-(1,1,5-trimethyl-hexylamino)-butan-2-ol di tosylate (B10)	G10

Preparation of acids

Acid 1 (A1)

3-(Methanesulfonyl-phenyl-amino)-benzoic acid (A1)

To a solution 3-(methanesulfonyl-phenyl-amino)-benzoic acid methyl ester (C1) (680 mg, 2.23 mmol, 1 equiv) in MeOH (5 ml) was added 2N aqueous NaOH solution (5 ml, 10 mmol, 4.5 equiv). The resulting mixture was stirred for 2 h then most of MeOH was removed *in vacuo*. The residue was diluted with H_2O and extracted with Et_2O. The aqueous layer was acidified using 2N aqueous HCl solution and the white precipitate formed was extracted twice with AcOEt. The combined organic solutions were dried over $MgSO_4$ and concentrated *in vacuo* to give 3-(methanesulfonyl-phenyl-amino)-benzoic acid (A1) (600 mg, 92%) as a white solid, which was used in the next step without further purification.

The following Acids were prepared in an analogous manner to that described for Acid 1 from the appropriate starting material:

Acid	Starting Material
3-(Dioxo-1λ^6-isothiazolidin-2-yl)-5-(methanesulfonyl-phenyl-amino)-benzoic acid (A2)	C2

3-(Methanesulfonyl-phenyl-amino)-5- *N*, *N*-dipropyl-isophthalamic acid (A3)	C3
3-Ethoxy-5-(methanesulfonyl-phenyl-amino)-benzoic acid (A4)	C4
3-(Methanesulfonyl-naphthalen-2-yl-amino)-benzoic acid (A5)	C5
Cyano-(methanesulfonyl-phenyl-amino)-benzoic acid (A7)	C7
3-(Methanesulfonyl-phenyl-amino)-2-methyl-benzoic acid (A10)	C10
3-(Methanesulfonyl-phenyl-amino)-4-methyl-benzoic acid (A11)	C11
4-Chloro-3-(methanesulfonyl-phenyl-amino)-benzoic acid (A12)	C12
3-(Methanesulfonyl-phenyl-amino)-5-methyl-benzoic acid (A13)	C13
3-(Methanesulfonyl-phenyl-amino)-5-methylsulfanyl-benzoic acid (A14)	C14
3-(Methanesulfonyl-phenyl-amino)-5-ethylsulfanyl-benzoic acid (A15)	C15

Acid 16

5-(Methanesulfonyl-phenyl-amino)-nicotinic acid (A16)

To a solution 5-(methanesulfonyl-phenyl-amino)-nicotinic acid ethyl ester (C16) (514 mg, 1.6 mmol, 1 equiv) in EtOH (50 ml) was added 2N aqueous NaOH solution (20 ml, 40 mmol, excess). The resulting mixture was stirred for 16 h then most of EtOH was removed *in vacuo*. The residue was partitioned between AcOEt and 5% citric acid aqueous solution (pH 4) and the two layers were separated. The aqueous phase was extracted with AcOEt and the combined organic solutions were dried over $MgSO_4$ then concentrated *in vacuo* to give 5-(methanesulfonyl-phenyl-amino)-nicotinic acid (A16) (130 mg, 28%) as a cream solid, which was used in the next step without further purification.

The following Acid was prepared in an analogous manner to that described for Acid 16 from the appropriate starting material:

Acid	**Starting Material**
2-(Methanesulfonyl-phenyl-amino)-isonicotinic acid (A17)	C17

The following Acids were prepared in an analogous manner to that described for Acid 1 from the appropriate starting material:

Acid	**Starting Material**
3-[(4-Fluoro-phenyl)-methanesulfonyl-amino]-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A18)	C18
3-[(3-Fluoro-phenyl)-methanesulfonyl-amino]-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A19)	C19
3-[(3-Methoxy-phenyl)-methanesulfonyl-amino]-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A20)	C20

3-[(4-Methoxy-phenyl)-methanesulfonyl-amino]-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A21)	C21
3-[(3,4-Difluoro-phenyl)-methanesulfonyl-amino]-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A22)	C22
3-[(3,5-Difluoro-phenyl)-methanesulfonyl-amino]-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A23)	C23
3-[(3-Cyano-phenyl)-methanesulfonyl-amino]-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A24)	C24
3-[(4-Cyano-phenyl)-methanesulfonyl-amino]-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A25)	C25
3-[(3-Carbamoyl-phenyl)-methanesulfonyl-amino]-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A26)	C26
3-[Methanesulfonyl-(4-trifluoromethyl-phenyl)-amino]-benzoic acid (A27)	C27
3-(Ethanesulfonyl-phenyl-amino)-benzoic acid (A28)	C28
3-[(Butane-1-sulfonyl)-phenyl-amino]-benzoic acid (A29)	C29
3-[Phenyl-(propane-2-sulfonyl)-amino]-benzoic acid (A30)	C30
2-Fluoro-3-(methanesulfonyl-phenyl-amino)-benzoic acid (A31)	C31
3-[Methanesulfonyl-(2-methoxy-phenyl)-amino]-benzoic acid (A33)	C33
3-[Methanesulfonyl-(3-methoxy-phenyl)-amino]-benzoic acid (A34)	C34
3-[Methanesulfonyl-(4-methoxy-phenyl)-amino]-benzoic acid (A35)	C35
3-[Methanesulfonyl-(2-chloro-phenyl)-amino]-benzoic acid (A36)	C36
3-[Methanesulfonyl-(3-chloro-phenyl)-amino]-benzoic acid (A37)	C37
3-[Methanesulfonyl-(4-chloro-phenyl)-amino]-benzoic acid (A38)	C38
3-[Methanesulfonyl-(3,4-dichloro-phenyl)-amino]-benzoic acid (A39)	C39
3-[Methanesulfonyl-(3,5-dichloro-phenyl)-amino]-benzoic acid (A40)	C40
3-[Methanesulfonyl-(2-cyano-phenyl)-amino]-benzoic acid (A41)	C41
3-[Methanesulfonyl-(3-cyano-phenyl)-amino]-benzoic acid (A42)	C42
3-[Methanesulfonyl-(4-cyano-phenyl)-amino]-benzoic acid (A43)	C43
3-Ethylamino-5-(methanesulfonyl-phenyl-amino)-benzoic acid (A49)	C49
3-(Methanesulfonyl-phenyl-amino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A51)	C51
Ethyl-(methanesulfonyl-phenyl-amino)1H-indole-5-carboxylic acid (A61)	C59

Acid 44

3-Bromo-5-(methanesulfonyl-phenyl-amino)-benzoic acid (A44)

A solution of 3-bromo-5-(methanesulfonyl-phenyl-amino)-benzoic acid *tert*-butyl ester (C44) (2 g, 4.7 mmol, 1 equiv) in CH_2Cl_2/CF_3COOH (1/1, 30 ml) was stirred at room temperature for 2 h then concentrated *in vacuo*. Traces of solvent were removed by azeotroping with toluene. The residue was triturated with Et_2O/*iso*-hexane (1:1) and filtered off to give 3-bromo-5-(methanesulfonyl-phenyl-amino)-benzoic acid (A44) (1.45 mg, 83%) as a white solid which was used in the next step without further purification.

The following Acids were prepared in an analogous manner to that described for Acid 44 from the appropriate starting material:

Acid	Starting Material
3-[(4-Fluoro-phenyl)-methanesulfonyl-amino]-benzoic acid (A6)	C6
3-[(3-Fluoro-phenyl)-methanesulfonyl-amino]-benzoic acid (A8)	C8
3-[(3,5-Difluoro-phenyl)-methanesulfonyl-amino]-benzoic acid (A9)	C9
4-Fluoro-3-(methanesulfonyl-phenyl-amino)-benzoic acid (A32)	C32
3-(Methanesulfonyl-naphthalen-1-yl-amino)-benzoic acid (A45)	C45
3-(Methanesulfonyl-pyridin-2-yl-amino)-benzoic acid (A46)	C46
3-(Methanesulfonyl-pyridin-3-yl-amino)-benzoic acid (A47)	C47
3-(Methanesulfonyl-pyridin-4-yl-amino)-benzoic acid (A48)	C48
3-(Benzyl-methyl-amino)-5-(methanesulfonyl-phenyl-amino)-benzoic acid (A50)	C50
3-Isobutyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid (A52)	C52
3-Ethynyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid (A53)	C53
(Methanesulfonyl-phenyl-amino)-methyl-biphenyl-3-carboxylic acid (A54)	C54
(Methanesulfonyl-phenyl-amino)-dimethyl-biphenyl-3-carboxylic acid (A55)	C55
3-Cyclopentyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid (A56)	C56
3-Cyclohexyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid (A57)	C57
3-(Methanesulfonyl-phenyl-amino)-5-(prop-1-ynyl)-benzoic acid (A58)	C58

Acid 59

3-Methanesulfonyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid (A59)

To a solution of 3-(methanesulfonyl-phenyl-amino)-5-methylsulfanyl-benzoic acid (A14) (67 mg, 0.199 mmol, 1 equiv) in MeOH/H_2O (3:1, 12 ml) was added oxone (488 mg, 0.79 mmol, 4 equiv). The resulting mixture was stirred at room temperature for 2 h and then concentrated *in vacuo*. The residue was partitioned between AcOEt and H_2O and the layers separated. The organic layer was washed with H_2O and brine, dried over

Na_2SO_4 and concentrated *in vacuo* to give a solid which was triturated with Et_2O to give 3-methanesulfonyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid (A59) (66 mg, 90%) as a white solid. $[M-H]^-$ = 368.0, RT = 2.64 min

Acid 60

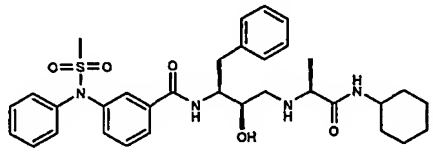
3-Ethanesulfonyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid (A60)

A60 was prepared in an analogous manner to that described for Acid 59 from 53 mg (0.15 mmol) of 3-(methanesulfonyl-phenyl-amino)-5-ethylsulfanyl-benzoic acid (A15) which yielded 56 mg (96%) of 3-ethanesulfonyl-5-(methanesulfonyl-phenyl-amino)-benzoic acid (A60) as a white solid. $[M-H]^-$ = 382.0, RT = 2.73 min

Preparation of Examples

Example 1

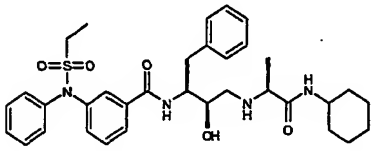
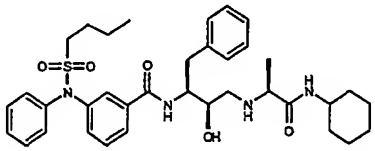
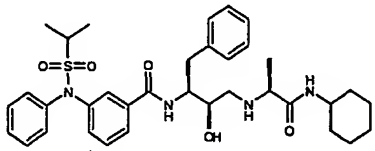
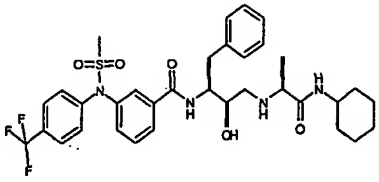
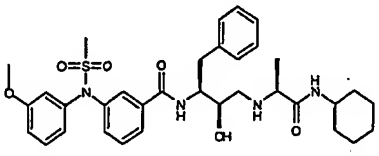
***N*-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-(methanesulfonyl-phenyl-amino)-benzamide (E1)**

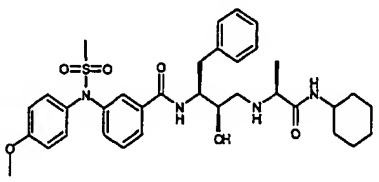
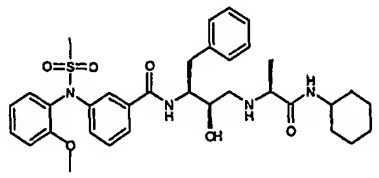
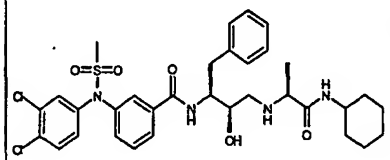
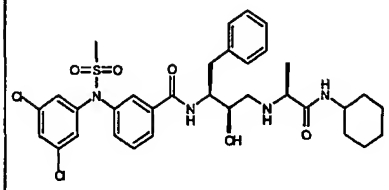
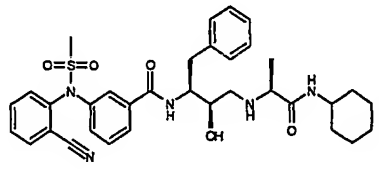
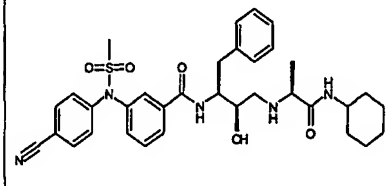


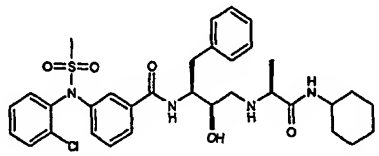
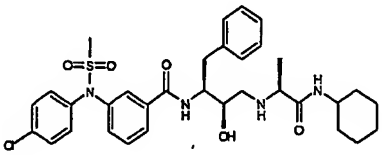
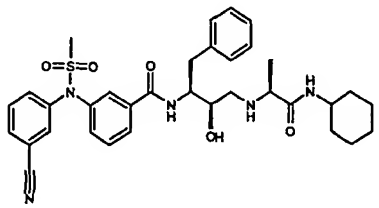
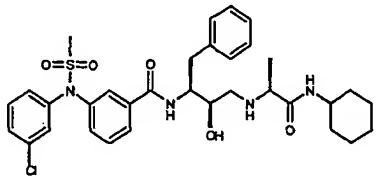
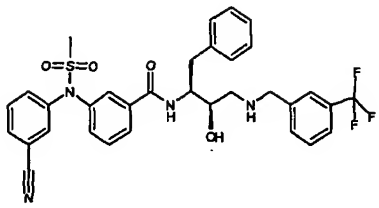
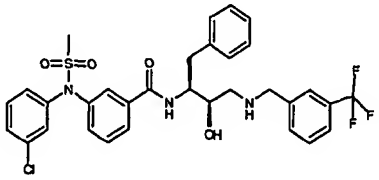
To a solution of 3-(methanesulfonyl-phenyl-amino)-benzoic acid (A1) (45 mg, 0.15 mmol, 1 equiv) in DMF (5 ml) at room temperature was added (S)-2-((2R,3S)-3-amino-2-hydroxy-4-phenyl-butylamino)- *N*-cyclohexyl-propionamide di-hydrogen chloride (B2) (63 mg, 0.15 mmol, 1 equiv), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (28 mg, 0.15 mmol, 1.2 equiv), 1-hydroxybenzotriazole hydrate (23 mg, 0.15 mmol, 1.2 equiv) and 4-ethylmorpholine (120 µl, 0.93 mmol, 6 equiv). The resulting mixture was stirred for 4 h then concentrated *in vacuo*. The residue was diluted with AcOEt and the organic phase washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by trituration with Et_2O to yield *N*-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-(methanesulfonyl-phenyl-amino)-benzamide (E1) as a white solid (46 mg, 50%).
$[M+H]^+$ = 607.2
RT = 2.63 min

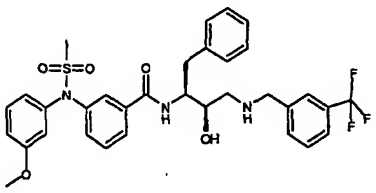
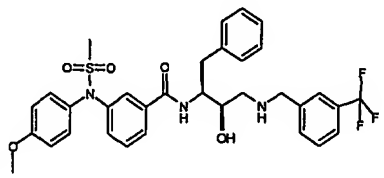
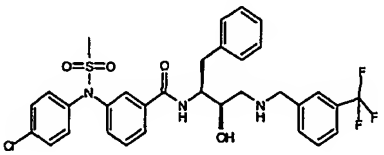
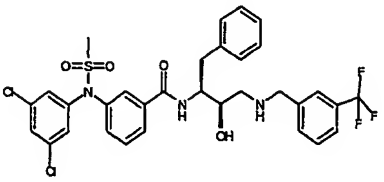
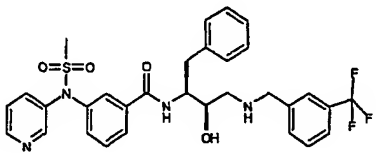
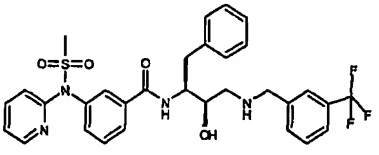
Examples 2-79 (E2-E79)

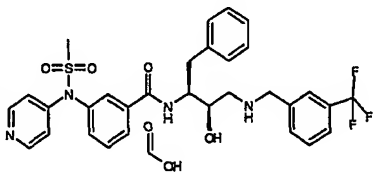
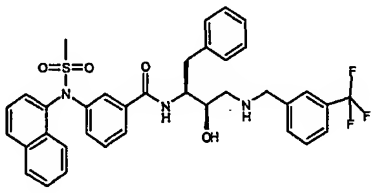
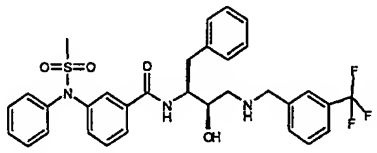
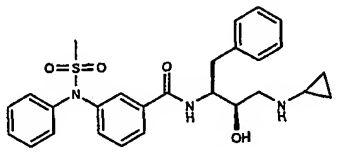
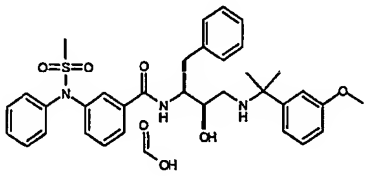
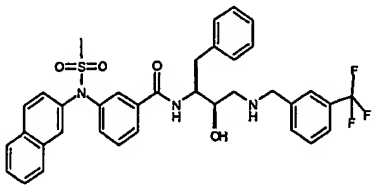
Examples 2-79 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

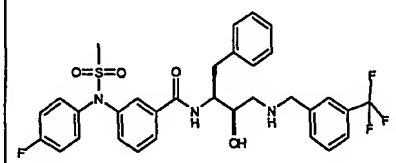
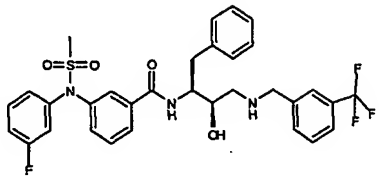
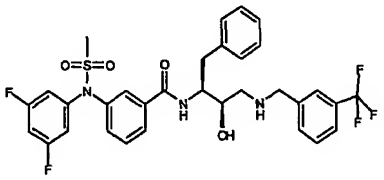
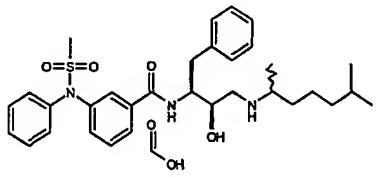
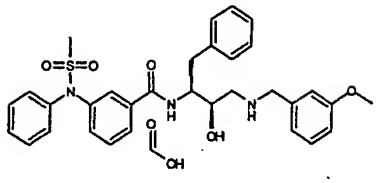
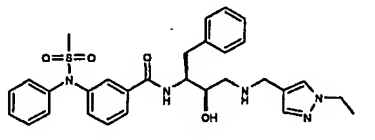
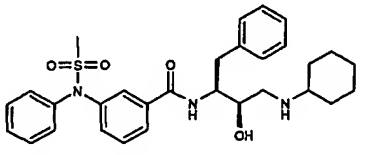
Example	Structure	Acid	Amine	$[M+H]^+$	RT (min)
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-(ethanesulfonyl-phenyl-amino)-benzamide (E2)		A28	B2	621.2	2.71
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-[(butane-1-sulfonyl)-phenyl-amino]-benzamide (E3)		A29	B2	649.2	2.90
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-[phenyl-(propane-2-sulfonyl)-amino]-benzamide (E4)		A30	B2	635.2	2.75
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-[methanesulfonyl-(4-trifluoromethyl-phenyl)-amino]-benzamide (E5)		A27	B2	675.3	2.84
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-[methanesulfonyl-(3-methoxy-phenyl)-amino]-benzamide (E6)		A34	B2	637.3	2.68

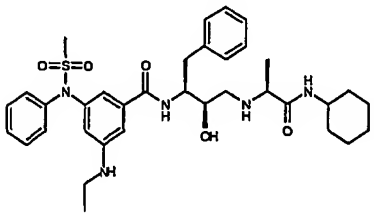
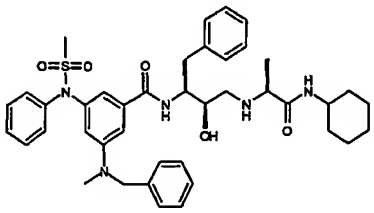
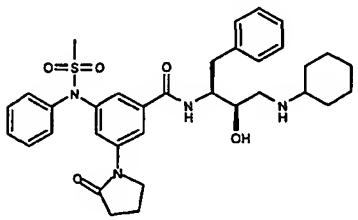
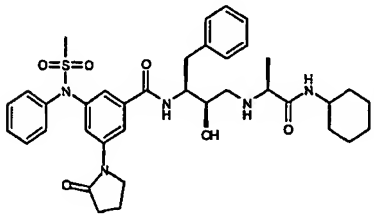
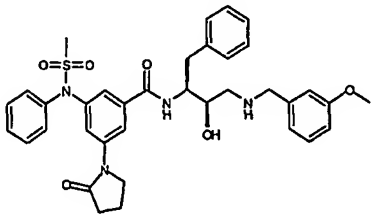
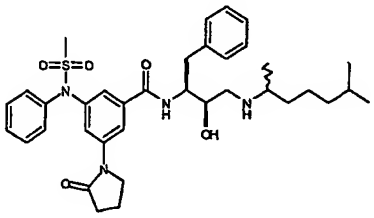
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-[methanesulfonyl-(4-methoxy-phenyl)-amino]-benzamide (E7)		A35	B2	637.2	2.66
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-[methanesulfonyl-(2-methoxy-phenyl)-amino]-benzamide (E8)		A33	B2	637.3	2.67
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-[(3,4-dichloro-phenyl)-methanesulfonyl-amino]-benzamide (E9)		A39	B2	675.2	2.90
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-[(3,5-dichloro-phenyl)-methanesulfonyl-amino]-benzamide (E10)		A40	B2	675.2	2.92
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-[(2-cyano-phenyl)-methanesulfonyl-amino]-benzamide (E11)		A41	B2	632.2	2.65
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-[(4-cyano-phenyl)-methanesulfonyl-amino]-benzamide (E12)		A43	B2	632.2	2.65

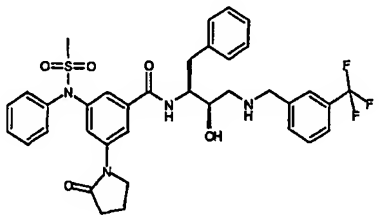
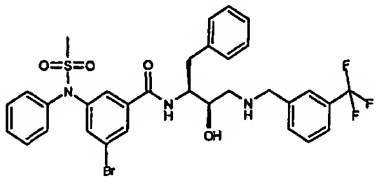
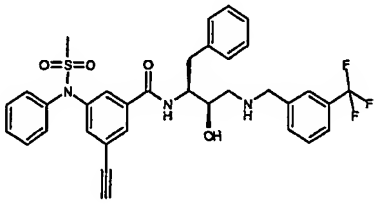
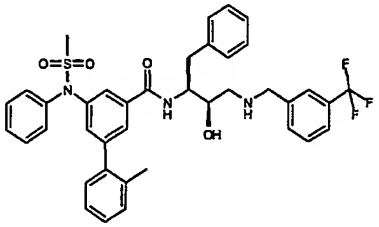
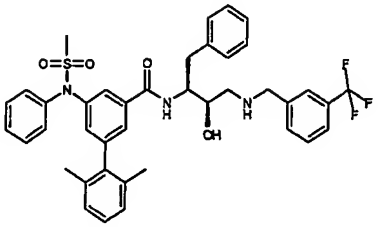
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-[(2-chloro-phenyl)-methanesulfonyl-amino]-benzamide (E13)		A36	B2	641.2	2.71
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-[(4-chloro-phenyl)-methanesulfonyl-amino]-benzamide (E14)		A38	B2	641.2	2.80
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-[(3-cyano-phenyl)-methanesulfonyl-amino]-benzamide (E15)		A42	B2	632.2	2.64
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-[(3-chloro-phenyl)-methanesulfonyl-amino]-benzamide (E16)		A37	B2	641.2	2.78
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-[(3-cyano-phenyl)-methanesulfonyl-amino]-benzamide (E17)		A42	B6	637.1	2.81
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-[(3-chloro-phenyl)-methanesulfonyl-amino]-benzamide (E18)		A37	B6	646.1	2.94

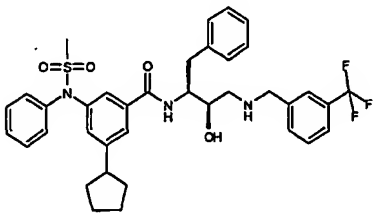
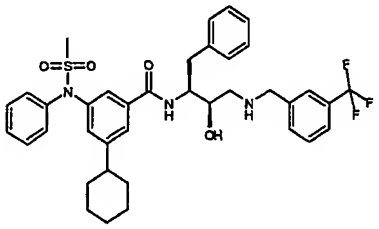
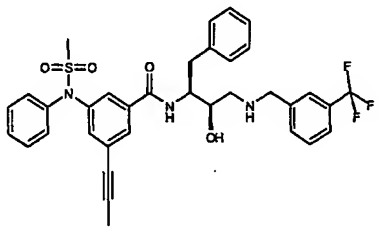
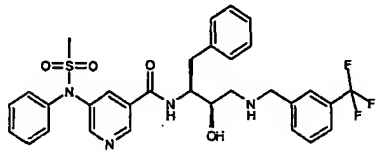
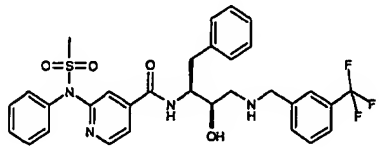
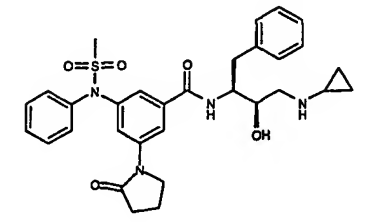
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-[methanesulfonyl-(3-methoxy-phenyl)-amino]-benzamide (E19)		A34	B6	642.2	2.85
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-[methanesulfonyl-(4-methoxy-phenyl)-amino]-benzamide (E20)		A35	B6	642.2	2.85
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-[(4-chloro-phenyl)-methanesulfonyl-amino]-benzamide (E21)		A38	B6	646.1	2.95
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-[(3,5-dichloro-phenyl)-methanesulfonyl-amino]-benzamide (E22)		A40	B6	680.1	3.07
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-(methanesulfonyl-pyridin-3-yl-amino)-benzamide (E23)		A47	B6	613.2	2.59
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-(methanesulfonyl-pyridin-2-yl-amino)-benzamide (E24)		A46	B6	613.1	2.83

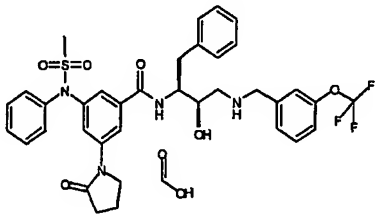
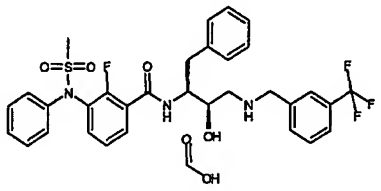
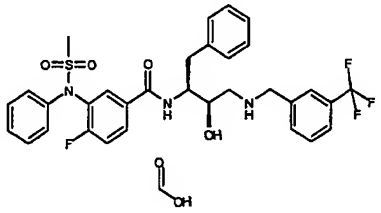
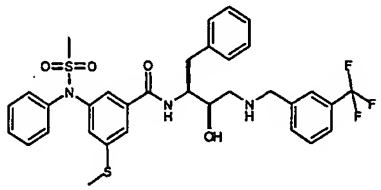
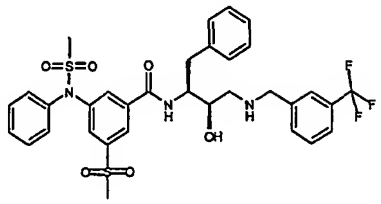
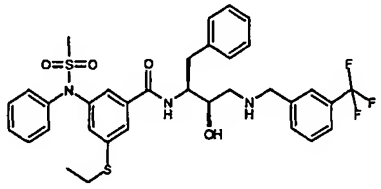
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-(methanesulfonyl-pyridin-4-yl-amino)-benzamide (E25)		A48	B6	613.2	2.61
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-(methanesulfonyl-naphthalen-1-yl-amino)-benzamide (E26)		A45	B6	662.2	3.08
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-(methanesulfonyl-phenyl-amino)-benzamide (E27)		A1	B6	612.1	2.74
N-((1S,2R)-1-Benzyl-3-cyclopropylamino-2-hydroxy-propyl)-(methanesulfonyl-phenyl-amino)-benzamide (E28)		A1	B8	494.1	2.47
N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[1-(3-methoxy-phenyl)-1-methyl-ethylamino]-propyl}-(methanesulfonyl-phenyl-amino)-benzamide formate salt (E29)		A1	B7	602.2	2.76
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-(methanesulfonyl-naphthalen-2-yl-amino)-benzamide (E30)		A5	B6	662.2	2.99

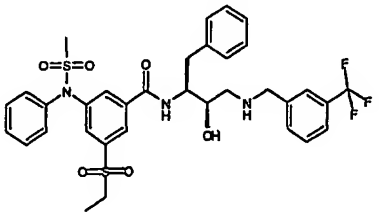
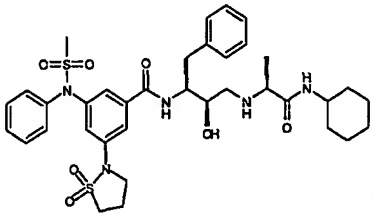
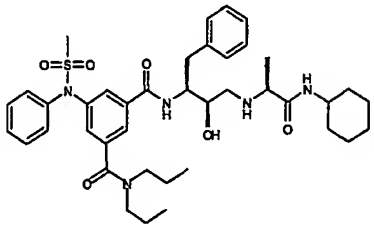
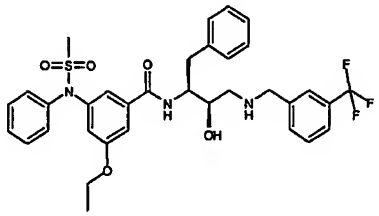
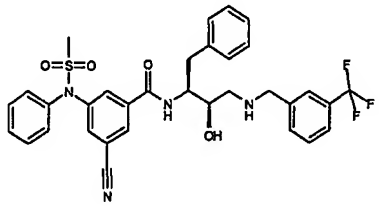
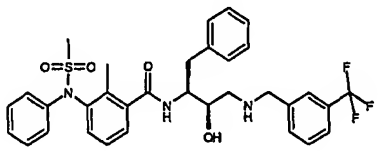
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-[(4-fluoro-phenyl)-methane sulfonyl-amino]-benzamide (E31)		A6	B6	630.2	2.84
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-[(3-fluoro-phenyl)-methane sulfonyl-amino]-benzamide (E32)		A8	B6	630.1	2.86
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-[(3,5-difluoro-phenyl)-methanesulfonyl-amino]-benzamide (E33)		A9	B6	648.2	2.92
N-[(1S,2R)-1-Benzyl-3-(1,5-dimethyl-hexylamino)-2-hydroxy-propyl]-(methanesulfonyl-phenyl-amino)-benzamide formate salt (E34)		A1	B3	566.3	2.83
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-(methanesulfonyl-phenyl-amino)-benzamide formate salt (E35)		A1	B4	574.2	2.62
N-{(1S,2R)-1-Benzyl-3-[(1-ethyl-1H-pyrazol-4-ylmethyl)-amino]-2-hydroxy-propyl}-(methanesulfonyl-phenyl-amino)-benzamide (E36)		A1	B9	562.5	2.33
N-((1S,2R)-1-Benzyl-3-cyclohexylamino-2-hydroxy-propyl)-(methanesulfonyl-phenyl-amino)-benzamide (E37)		A1	B1	536.3	2.57

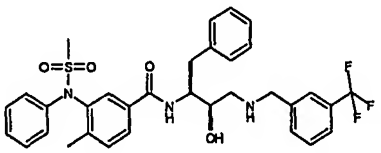
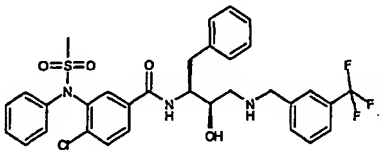
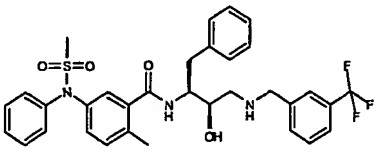
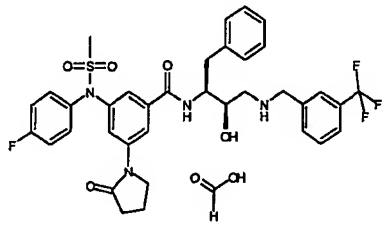
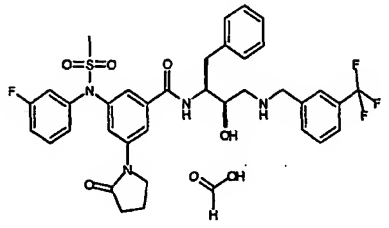
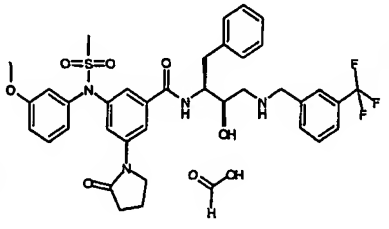
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-ethylamino-(methanesulfonyl-phenyl-amino)-benzamide (E38)		A49	B2	650.2	2.7
N-[(1S,2R)-Benzyl-((S)-1-cyclohexylcarbamoyl-ethylamino)-hydroxy-propyl]-(benzyl-methyl-amino)-(methanesulfonyl-phenyl-amino)-benzamide (E39)		A50	B2	726.3	2.95
N-((1S,2R)-1-Benzyl-3-cyclohexylamino-2-hydroxy-propyl)-(methanesulfonyl-phenyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzamide (E40)		A51	B1	-	3.14
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-(methanesulfonyl-phenyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzamide (E41)		A51	B2	690.2	2.61
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-(methanesulfonyl-phenyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzamide (E42)		A51	B4	657.3	2.59
N-[(1S,2R)-1-Benzyl-3-(1,5-dimethyl-hexylamino)-2-hydroxy-propyl]-(methanesulfonyl-phenyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzamide (E43)		A51	B3	649.3	2.81

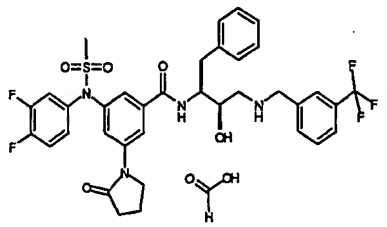
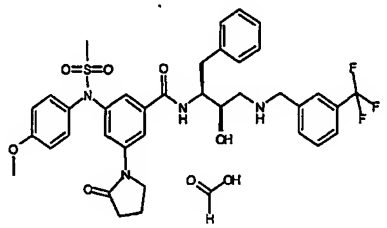
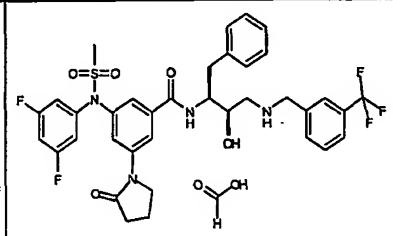
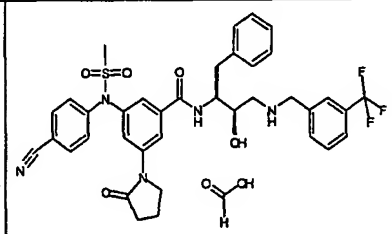
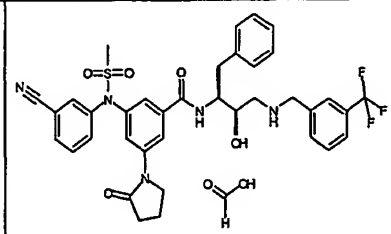
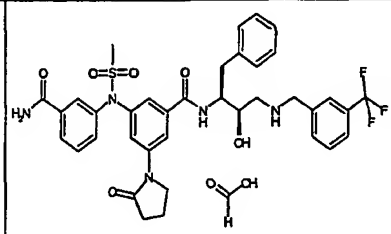
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-(methanesulfonyl-phenyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzamide (E44)		A51	B6	637.2	2.66
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-bromo-(methanesulfonyl-phenyl-amino)-benzamide (E45)		A44	B6	692.2	2.96
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-ethynyl-(methanesulfonyl-phenyl-amino)-benzamide (E46)		A53	B6	636.2	2.91
(Methanesulfonyl-phenyl-amino)-methyl-biphenyl-3-carboxylic acid [(1S,2R)-1-benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-amide (E47)		A54	B6	702.2	3.13
(Methanesulfonyl-phenyl-amino)-dimethyl-biphenyl-3-carboxylic acid [(1S,2R)-1-benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-amide (E48)		A55	B6	716.3	3.18

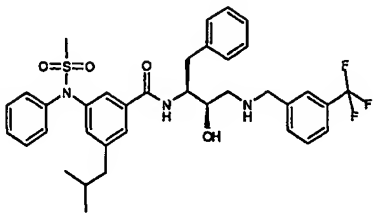
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-cyclopentyl-(methanesulfonyl-phenyl-amino)-benzamide (E49)		A56	B6	680.3	3.13
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-cyclohexyl-(methanesulfonyl-phenyl-amino)-benzamide (E50)		A57	B6	612.2	3.19
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-(methanesulfonyl-phenyl-amino)-prop-1-ynyl-benzamide (E51)		A58	B6	650.2	2.97
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-(methanesulfonyl-phenyl-amino)-nicotinamide (E52)		A16	B6	613.2	2.69
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-#C!-(methanesulfonyl-phenyl-amino)-isonicotinamide (E53)		A17	B6	613.2	2.75
N-((1S,2R)-1-Benzyl-3-cyclopropylamino-2-hydroxy-propyl)-(methanesulfonyl-phenyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzamide (E54)		A51	B8	494.1	2.47

N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethoxy-benzylamino)-propyl]-(methanesulfonyl-phenyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzamide formate salt (E55)		A51	B5	711.2	2.91
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-*C*-fluoro-(methanesulfonyl-phenyl-amino)-benzamide formate salt (E56)		A31	B6	630.1	2.82
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-fluoro-(methanesulfonyl-phenyl-amino)-benzamide formate salt (E57)		A32	B6	630.1	2.88
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-(methanesulfonyl-phenyl-amino)-methylsulfanyl-benzamide (E58)		A14	B6	658.2	3.01
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-methanesulfonyl-(methanesulfonyl-phenyl-amino)-benzamide (E59)		A59	B6	690.2	2.81
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-ethylsulfanyl-(methanesulfonyl-phenyl-amino)-benzamide (E60)		A15	B6	672.1	3.06

N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-ethanesulfonyl-(methanesulfonyl-phenyl-amino)-benzamide (E61)		A60	B6	704.2	2.86
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-(methanesulfonyl-phenyl-amino)-benzamide (E62)		A2	B2	726.3	2.60
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-(methanesulfonyl-phenyl-amino)-*N'*-*N'*-dipropyl-isophthalamide (E63)		A3	B2	734.3	2.85
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-ethoxy-(methanesulfonyl-phenyl-amino)-benzamide (E64)		A4	B6	656.3	2.70
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-cyano-(methanesulfonyl-phenyl-amino)-benzamide (E65)		A7	B6	637.1	2.86
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-(methanesulfonyl-phenyl-amino)-*C*-methyl-benzamide (E66)		A10	B6	626.2	2.80

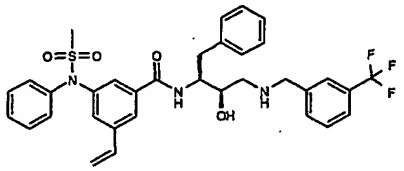
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-(methanesulfonyl-phenyl-amino)-methyl-benzamide (E67)		A11	B6	626.3	2.91
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-chloro-(methanesulfonyl-phenyl-amino)-benzamide (E68)		A12	B6	646.1	3.09
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-(methanesulfonyl-phenyl-amino)-*C*-methyl-benzamide (E69)		A13	B6	626.3	2.83
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-[(4-fluoro-phenyl)-methane sulfonyl-amino]-(2-oxo-pyrrolidin-1-yl)-benzamide formate salt (E70)		A18	B6	713.2	2.87
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-[(3-fluoro-phenyl)-methane sulfonyl-amino]-(2-oxo-pyrrolidin-1-yl)-benzamide formate salt (E71)		A19	B6	713.2	2.86
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-[(3-methoxy-phenyl)-methanesulfonyl-amino]-(2-oxo-pyrrolidin-1-yl)-benzamide formate salt (E72)		A20	B6	725.2	2.84

N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-[(3,4-difluoro-phenyl)-methanesulfonyl-amino]-(2-oxo-pyrrolidin-1-yl)-benzamide formate salt (E73)		A22	B6	731.2	3.17
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-[methanesulfonyl-(4-methoxy-phenyl)-amino]-(2-oxo-pyrrolidin-1-yl)-benzamide formate salt (E74)		A21	B6	725.2	3.06
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-[(3,5-difluoro-phenyl)-methanesulfonyl-amino]-(2-oxo-pyrrolidin-1-yl)-benzamide formate salt (E75)		A23	B6	731.1	2.94
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-[(4-cyano-phenyl)-methanesulfonyl-amino]-(2-oxo-pyrrolidin-1-yl)-benzamide formate salt (E76)		A25	B6	720.1	2.81
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-[(3-cyano-phenyl)-methanesulfonyl-amino]-(2-oxo-pyrrolidin-1-yl)-benzamide formate salt (E77)		A24	B6	720.1	2.82
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-[(3-formamide-phenyl)-methanesulfonyl-amino]-(2-oxo-pyrrolidin-1-yl)-benzamide formate salt (E78)		A26	B6	738.1	2.58

N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-isobutyl-(methanesulfonyl-phenyl-amino)-benzamide (E79)		A52	B6	668.2	3.11

Example 80

***N*-[(1S,2R)-Benzyl-hydroxy-(3-trifluoromethyl-benzylamino)-propyl]-3-(methanesulfonyl-phenyl-amino)-5-vinyl-benzamide (E80)**



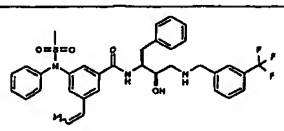
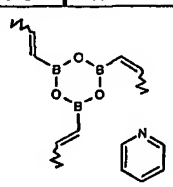
To a solution of *N*-[(1S,2R)-benzyl-hydroxy-(3-trifluoromethyl-benzylamino)-propyl]-3-bromo-5-(methanesulfonyl-phenyl-amino)-benzamide (E45) (140 mg, 0.2 mmol, 1 equiv) in DME (0.7 ml) and H_2O (0.6 ml) was added tetrakis(triphenylphosphine)-palladium(0) (12 mg, 0.01 mmol, 0.05 equiv), and the suspension was stirred for 10 min. 2,4,6 Trivinylcyclotriboroxane-pyridine complex (49 mg, 0.2 mmol, 1 equiv) in DME (1.3 ml) and K_2CO_3 (28 mg, 0.2 mmol, 1 equiv) were added and the resulting mixture was stirred at 90°C for 1 h, cooled to room temperature and diluted with AcOEt. The organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH : 96/4) gave *N*-[(1S,2R)-benzyl-hydroxy-(3-trifluoromethyl-benzylamino)-propyl]-3-(methanesulfonyl-phenyl-amino)-5-vinyl-benzamide (E80) (100 mg, 77%) as a pale yellow foam.

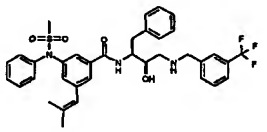
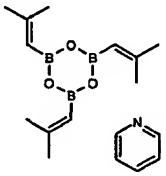
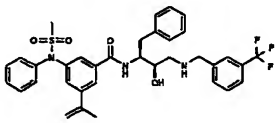
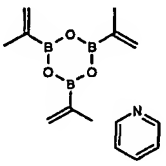
$[M+H]^+$ = 638.2

RT = 2.92 min

Examples 81-83 (E81-E83)

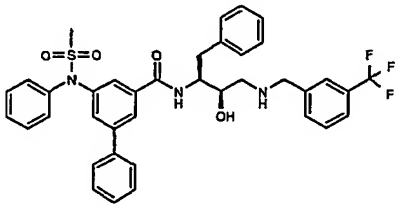
Examples 81-83 were prepared in an analogous manner to Example 80 from Example 45 (E45) and the appropriate vinylcyclotriboroxane-pyridine complex (as described by F. Kerins and D. F. O' Shea in *J. Org. Chem*, **2002**, *67*, 4968-4971):

Example	Structure	Boroxane Complex	$[M+H]^+$	RT (min)
N-[(1S,2R)-Benzyl-hydroxy-(3-trifluoromethyl-benzylamino)-propyl]-(methanesulfonyl-phenyl-amino)-(Z/E)-propenyl-			652.3	2.92

benzamide (E81)				
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-3-(methanesulfonyl-phenyl-amino)-5-(2-methyl-propenyl)-benzamide (E82)			666.3	2.96
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-3-isopropenyl-5-(methanesulfonyl-phenyl-amino)-benzamide (E83)			652.2	2.77

Example 84

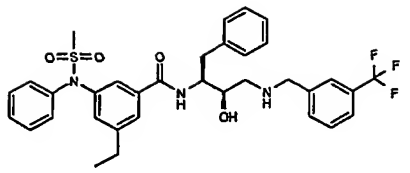
5-(Methanesulfonyl-phenyl-amino)-biphenyl-3-carboxylic acid [(1S,2R)-1-benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-amide (E84)



To a solution of *N*-[(1S,2R)-benzyl-hydroxy-(3-trifluoromethyl-benzylamino)-propyl]-3-bromo-5-(methanesulfonyl-phenyl-amino)-benzamide (E45) (140 mg, 0.2 mmol, 1 equiv) in toluene (10 ml) were added palladium(II)acetate (2 mg, 0.01 mmol, 0.05 equiv), phenylboronic acid (29 mg, 0.24 mmol, 1.2 equiv), 2-(dicyclohexylphosphino)biphenyl (7 mg, 0.02 mmol, 0.1 equiv) and K_3PO_4 (127 mg, 0.6 mmol, 3 equiv) and the resulting mixture was stirred at 100°C for 16 h, cooled to room temperature and diluted with AcOEt. The organic phase was washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel gave 5-(methanesulfonyl-phenyl-amino)-biphenyl-3-carboxylic acid [(1S,2R)-1-benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-amide (E84) (84 mg, 61%) as a pale yellow oil.
$[M+H]^+$ = 688.2
RT = 3.10 min

Example 85

***N*-[(1S,2R)-Benzyl-hydroxy-(3-trifluoromethyl-benzylamino)-propyl]-3-ethyl-5-(methanesulfonyl-phenyl-amino)-benzamide (E85)**



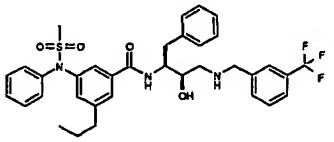
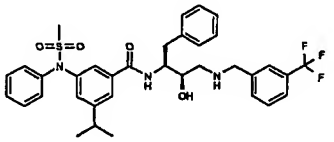
A flask was charged with *N*-[(1S,2R)-benzyl-hydroxy-(3-trifluoromethyl-benzylamino)-propyl]-3-(methanesulfonyl-phenyl-amino)-5-vinyl-benzamide (E80) (100 mg, 0.16 mmol, 1 equiv), 10% palladium on charcoal (50% wet, 100 mg, 50% w/w), NH_4COOH (99 mg, 1.6 mmol, 10 equiv) H_2O (2 ml) and EtOH (10 ml). The resulting mixture was stirred at 50°C for 4 h, cooled to room temperature and the catalyst was filtered off through a pad of celite. Most of the EtOH was removed *in vacuo* and the residue diluted with H_2O and AcOEt. The layers were separated. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give *N*-[(1S,2R)-benzyl-hydroxy-(3-trifluoromethyl-benzylamino)-propyl]-3-ethyl-5-(methanesulfonyl-phenyl-amino)-benzamide (E85) (70 mg, 70%) as a white solid.

$[M+H]^+$ = 640.3

RT = 2.86 min

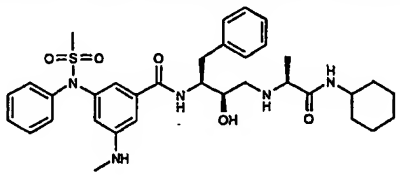
Examples 86-87 (E86-E87)

Examples 86-87 were prepared in an analogous manner to that described for Example 85 (E85) from the appropriate starting material:

Example	Structure	Starting Material	$[M+H]^+$	RT (min)
N-[(1S,2R)-Benzyl-hydroxy-(3-trifluoromethyl-benzylamino)-propyl]-3-(methanesulfonyl-phenyl-amino)-5-propyl-benzamide (E86)		E81	654.2	2.81
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-3-isopropyl-5-(methanesulfonyl-phenyl-amino)-benzamide (E87)		E83	654.2	2.78

Example 88

N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-3-(methanesulfonyl-phenyl-amino)-5-methylamino-benzamide (E88)

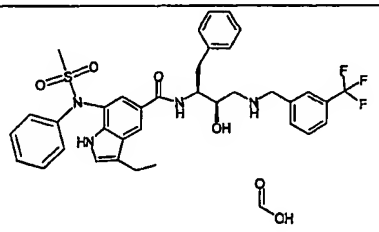
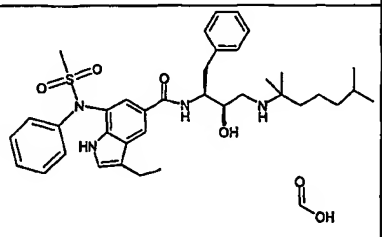


A flask was charged with *N*-[(1S,2R)-benzyl-((S)-1-cyclohexylcarbamoyl-ethylamino)-hydroxy-propyl]-(benzyl-methyl-amino)-(methanesulfonyl-phenyl-amino)-benzamide (E39) (50 mg, 0.07 mmol, 1 equiv), 10% palladium on charcoal (50% wet, 5 mg, 5% w/w), NH_4COOH (44 mg, 0.7 mmol, 10 equiv), H_2O (2 ml) and EtOH (10 ml). The resulting mixture was stirred at 50°C for 3 h, cooled to room temperature and the catalyst was filtered off through a pad of celite. Most of the EtOH was removed *in vacuo* and the residue diluted with saturated $NaHCO_3$ aqueous solution and AcOEt. The layers were separated. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo.* The residue was triturated with Et_2O to give *N*-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-3-(methanesulfonyl-phenyl-amino)-5-methylamino-benzamide (E88) (18 mg, 41%) as a white solid.

$[M+H]^+$ = 636.2, RT = 2.62 min

Examples 89-90 (E89-E90)

Examples 89-90 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Structure	Acid	Amine	$[M+H]^+$	RT (min)
Ethyl-(methanesulfonyl-phenyl-amino)-1*H*-indole-5-carboxylic acid [(1S,2R)-1-benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-amide formate salt (E89)		A61	B6	679.5	2.88
Ethyl-(methanesulfonyl-phenyl-amino)-1*H*-indole-5-carboxylic acid [(1S,2R)-1-benzyl-2-hydroxy-3-(trimethyl-hexylamino)-propyl]-amide formate salt		A61	B10	647.6	2.93

(E90)					

Compounds of the invention may be tested for *in vitro* biological activity in accordance with the following assays:

(I) Asp-2 inhibitory assay

For each compound being assayed, in a 384 well plate, is added:-

a) 1μl of a DMSO solution of the test compound (IC_{50} curve uses ten 1 in 2 serial dilutions from 500 μM).

b) 10 μl of substrate (FAM-[SEVNLDAEFK]-TAMRA) solution in buffer. This is prepared by diluting 2ml of a 2mM DMSO solution of the substrate into 400ml of buffer (100mM Sodium acetate pH = 4.5, 1 l Milli-Q water, 0.06% Triton X-100 (0.5 ml/l) , pH adjusted to 4.5 using glacial acetic acid). Aminomethyl fluorescein (FAM) and tetramethyl rhodamine (TAMRA) are fluorescent molecules which co-operate to emit fluorescence at 535nm upon cleavage of the SEVNLDAEFK peptide.

c) 10 μl enzyme solution. This is prepared by diluting 16ml of a 500nM enzyme solution into 384 ml of buffer (prepared as above).

Blank wells (enzyme solution replaced by buffer) are included as controls on each plate. Wells are incubated for 1h at room temperature and fluorescence read using a Tecan Ultra Fluorimeter/Spectrophotometer (485nm excitation, 535nm emission).

(II) Cathepsin D inhibitory assay

For each compound being assayed, in a 384 well plate, is added:-

a) 1μl of a DMSO solution of the test compound (IC_{50} curve uses ten 1 in 2 serial dilutions from 500 μM).

b) 10 μl of substrate (FAM-[SEVNLDAEFK]-TAMRA) solution in buffer. This is prepared by diluting 2ml of a 2mM DMSO solution of the substrate into 400ml of buffer (100mM Sodium acetate pH = 4.5, 1 l Milli-Q water, 0.06% Triton X-100 (0.5 ml/l) , pH adjusted to 4.5 using glacial acetic acid).

c) 10 μl enzyme solution. This is prepared by diluting 1.6ml of a 200 unit/ml (in 10 mM HCl) enzyme solution into 398.4 ml of buffer (prepared as above).

Blank wells (enzyme solution replaced by buffer) are included as controls on each plate. Wells are incubated for 1h at room temperature and fluorescence read using a Tecan Ultra Fluorimeter/Spectrophotometer (485nm excitation, 535nm emission).

Pharmacological Data

The compounds of E1-E90 were tested in Assays (I) and (II) and exhibited inhibition within the following range: 1-5000 nM (Asp-2) and 50-25000 nM (CatD). More particularly, the compounds of E17, 25, 38, 41, 46, 49, 50, 55-56, 60, 61, 64, 77, 83 and 87 exhibited inhibition within the following range: 1-100 nM (Asp-2) and 200-2500 nM

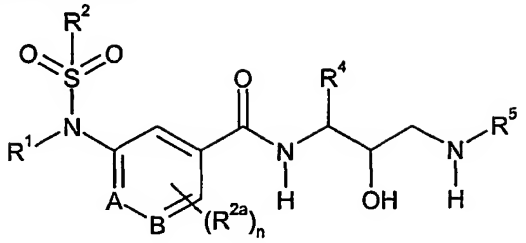
(CatD). Most particularly, the compounds of E38, 41, 49, 55, 60, 64, 77 and 87 exhibited inhibition within the following range: 1-10 nM (Asp-2) and 400-1000 nM.

Abbreviations

DMF	dimethylformamide
DMSO	dimethylsulfoxide
DMAP	dimethylaminophenol
DABCO	1,4-diazabicyclo [2.2.2] octane
DME	dimethyl ether
THF	tetrahydrofuran
HOBT	N-hydroxybenzotriazole
FAM	carboxyfluorescein
TAMRA	carboxytetramethylrhodamine
[ ]	single amino acid letter code relating to peptide sequence

Claims

1. A compound of formula (I):



(I)

wherein

R^1 represents aryl or heteroaryl;

R^2 represents C_{1-6} alkyl or C_{3-8} cycloalkyl;

R^{2a} represents hydrogen, halogen, C_{1-3} alkyl or C_{1-3} alkoxy;

n represents 0, 1 or 2;

A represents –C(H)=, -C(R^{2b})= or –N=;

R^{2b} represents C_{1-3} alkyl, C_{2-4} alkenyl, halogen, C_{1-3} alkoxy, amino, cyano or hydroxy;

B represents –C(R^3)= or –N=;

R^3 represents hydrogen, halogen, optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl, -C_{2-6} alkenyl-aryl, -C_{2-6} alkenyl-heteroaryl, -C_{2-6} alkenyl-heterocyclyl, C_{3-8} cycloalkyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, cyano, azido, nitro, sulphoxide, –NR^7R^8, -NR^9COR^{10}, -$NR^{11}SO_2R^{12}$, -$NR^{11}CO_2R^{12}$, -OR^{13}, -SO_2R^{14}, -SR^{15}, -C≡CR^{16}, -C_{0-6} alkyl-$(CF_2)_qCF_3$, -$CONR^{17}R^{18}$, $COOR^{19}$, -C_{1-6} alkyl-$NR^{20}R^{21}$ or -C_{1-6} alkyl-N_3, or R^3 together with R^{2b} on adjacent carbon atoms may form a fused 5-7 membered saturated or partially saturated carbocyclic or heterocyclic ring optionally substituted by a C_{1-6} alkyl group;

R^4 represents optionally substituted C_{1-6} alkyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl or -C_{1-6} alkyl-heterocyclyl;

R^5 represents hydrogen, optionally substituted C_{1-10} alkyl, -C_{3-8} cycloalkyl, -C_{3-8} cycloalkenyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, -C_{3-8} cycloalkyl-aryl, -heterocyclyl-aryl, -C_{1-6} alkyl-aryl-heteroaryl, -C(R^aR^b)-CONH-C_{1-6} alkyl, -C(R^cR^d)-CONH-C_{3-8} cycloalkyl, -C_{2-6} alkyl-S-C_{1-6} alkyl, -C_{2-6} alkyl-NR^eR^f, -C(R^gR^h)-C_{1-6} alkyl, -C(R^iR^j)-aryl, -C(R^kR^l)-C_{1-6} alkyl-aryl, -C(R^mR^n)-C_{1-6} alkyl-heteroaryl, -C(R^oR^p)-C_{1-6} alkyl-heterocyclyl, -C_{1-6} alkyl-O-C_{1-6} alkyl-aryl, -C_{1-6} alkyl-O-C_{1-6} alkyl-heteroaryl or -C_{1-6} alkyl-O-C_{1-6} alkyl-heterocyclyl;

R^7, R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20} and R^{21} independently represent hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, -CO-C_{1-6} alkyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl or -C_{1-6} alkyl-heterocyclyl;

R^a, R^c, R^e, R^f, R^g, R^h, R^i, R^j, R^k, R^l, R^m, R^n, R^o and R^p independently represent hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl;

R^b and R^d independently represent hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl or -C_{1-6} alkyl-SO_2-C_{1-6} alkyl or R^a and R^b, R^c and R^d, R^g and R^h, R^i and R^j, R^k and R^l and R^m and R^n together with the carbon atom to which they are attached may form a C_{3-8} cycloalkyl group;

R^{12} represents C_{1-6} alkyl or C_{3-8} cycloalkyl;

q represents 0 to 3;

optional substituents for alkyl groups of R^3, R^4 and R^5 include one or more (eg. 1, 2 or 3) halogen, C_{1-6} alkoxy, amino, cyano or hydroxy groups;

and wherein said aryl, heteroaryl or heterocyclyl groups may be optionally substituted by one or more (eg. 1, 2 or 3) C_{1-6} alkyl, halogen, -CF_3, -OCF_3, =O, hydroxy, C_{1-6} alkoxy, C_{2-6} alkynyl, C_{2-6} alkenyl, amino, cyano, nitro, -$NR^{22}COR^{23}$, –$CONR^{22}R^{23}$ -C_{1-6} alkyl-NR^{22} R^{23} (wherein R^{22} and R^{23} independently represent hydrogen or C_{1-6} alkyl), -C_{1-6} alkyl-O-C_{1-6} alkyl or -C_{1-6} alkanoyl groups;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1 which is a compound of formula E1-E90 or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof in admixture with one or more pharmaceutically acceptable diluents or carriers.

4. A compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof for use as a pharmaceutical.

5. Use of a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof in the treatment of diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

6. Use of a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

7. A method of treatment or prophylaxis of diseases characterised by elevated β-amyloid levels or β-amyloid deposits which comprises administering to a patient an effective amount of a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof.

8. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof for use in

the treatment of diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

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(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DEMONT, Emmanuel, Hubert** [FR/GB]; GlaxoSmithKline, The Frythe, Welwyn Hertfordshire AL6 9AR (GB). **REDSHAW, Sally** [GB/GB]; GlaxoSmithKline, The Frythe, Welwyn Hertfordshire AL6 9AR (GB). **WALTER, Daryl, Simon** [GB/GB]; GlaxoSmithKline, The Frythe, Welwyn Hertfordshire AL6 9AR (GB).

(74) Agent: **GIBSON, Mark**; GlaxoSmithKline (CN925.1), 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

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(54) Title: HYDROXYETHYLAMINE COMPOUNDS HAVING ASP2 INHIBITORY ACTIVITY FOR THE TREATMENT OF ALZHEIMER'S DISEASE

(57) Abstract: The present invention relates to novel hydroxyethylamine compounds having Asp2 (β-secretase, BACE1 or Memapsin) inhibitory activity, processes for their preparation, to compositions containing them and to their use in the treatment of diseases characterised by elevated β- amyloid levels or β-amyloid deposits, particularly Alzheimer's disease.

WO 2004/080376 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/002644

A. CLASSIFICATION OF SUBJECT MATTER
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C07D213/75 C07D231/12 A61K31/18 A61K31/275 A61K31/402
A61K31/404 A61K31/415 A61K31/425 A61K31/4402 A61K31/4406

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/02505 A (ELAN PHARM INC) 10 January 2002 (2002-01-10) cited in the application page 69, line 31 - page 76, line 31; claim 1	1-8

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
18 August 2004	21/09/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cooper, S

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/002644

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/002644

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 7 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/002644

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